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<p>(21) International Application Number: PCT/JP93/01082</p> <p>(22) International Filing Date: 3 August 1993 (03.08.93)</p> <p>(30) Priority data: 4/221359 20 August 1992 (20.08.92) JP</p> <p>(71) Applicant (for all designated States except US): OTSUKA PHARMACEUTICAL COMPANY, LIMITED [JP/JP]; 9, Kandatsukasa-cho 2-chome, Chiyoda-ku, Tokyo 101 (JP).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (for US only) : OGAWA, Hidenori [JP/JP]; 25-18, Nakakirai-Aza-Nakasenishinokoshi, Matsushige-cho, Itano-gun, Tokushima 771-02 (JP). KONDO, Kazumi [JP/JP]; 55-11, Nakakirai-Aza-Inamoto, Matsushige-cho, Itano-gun, Tokushima 771-02 (JP). YAMASHITA, Hiroshi [JP/JP]; 57-1, Sasakino-Aza-Hachikami, Matsushige-cho, Itano-gun, Tokushima 771-02 (JP). KAN, Keizo [JP/JP]; 463-10, Kagasuno, Kawauchi-cho, Tokushima-shi, Tokushima 771-01 (JP). TOMINAGA, Michiaki [JP/JP]; 310-6, Takaiso, Kamiita-cho, Itano-gun, Tokushima 771-13 (JP). YABUUCHI, Yoichi [JP/JP]; 900-25, Omatsu, Kawauchi-cho, Tokushima-shi, Tokushima 771-01 (JP).</p>		<p>(74) Agents: AOYAMA, Tamotsu et al.; Twin 21 Mid Tower, 1-61, Shiromi 2-chome, Chuo-ku, Osaka-shi, Osaka 540 (JP).</p> <p>(81) Designated States: AU, CA, KR, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p>Published With international search report.</p>
<p>(54) Title: BENZOHETEROCYCLIC COMPOUNDS AS OXYTOCIN AND VASOPRESSIN ANTAGONISTS</p> <div style="text-align: center; margin: 20px 0;"> <p>(1)</p> </div> <p>(57) Abstract</p> <p>Novel benzoheterocyclic compound of formula (1) and pharmaceutically acceptable salts thereof, which show excellent antivasopressin activity and oxytocin antagonistic activity, and are useful as a vasopressin antagonist or oxytocin antagonist. A is a 5- or 6-membered unsaturated heterocyclic residue having 1 to 2 heteroatoms. B1 and B2 are each methylene or a group of the formula: -NR8- (wherein R8 is a hydrogen atom or a lower alkyl group).</p>		

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## DESCRIPTION

## Benzoheterocyclic compounds as oxytocin and vasopressin antagonists

5            Technical Field

The invention relates to novel benzoheterocyclic compounds which are useful as medicines.

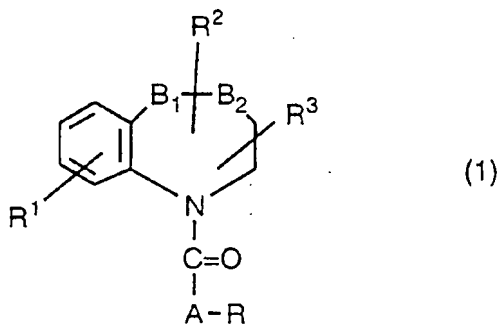
Background Art

10            Various benzoheterocyclic compounds analogous to the compounds of the present invention have been known to have anti-vasopressin activities in European Patent Publication 0382185 (published on August 15, 1990), WO 91/05549 (published on May 2, 1991), and WO 91/16916 (published on November 14, 1991). These known compounds are similar to the compounds of the present invention in the benzoheterocyclic nucleus of the chemical structure but are different from the compounds of the present invention in the substituent at 1-position and in the anti-vasopressin activities to some extent.

Disclosure of the Invention

15            An object of the present invention is to provide benzoheterocyclic compounds of the formula (1):

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wherein R¹ is hydrogen atom or a halogen atom,

R² is hydrogen atom, oxo group, a lower alkylidene group, hydroxy group, a lower alkoxy group, a lower alkenyloxy group, a hydroxy-substituted lower alkoxy group, a lower alkoxycarbonyl-substituted lower alkoxy group, a

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carboxy-substituted lower alkoxy group, a lower alkylsulfonyloxy-substituted lower alkoxy group, a phthalimide-substituted lower alkoxy group, a hydroxy-substituted lower alkyl group, a group of the formula:  $-O-D-(CO)_lNR^4R^5$

(wherein D is a lower alkylene group, l is 0 or 1,  $R^4$  and  $R^5$  are the same or

5 different and are hydrogen atom, a lower alkyl group, a lower alkanoyl group, a cycloalkyl group, or an amino-substituted lower alkyl group which may optionally have a lower alkyl substituent, or  $R^4$  and  $R^5$  may combine together with the nitrogen atom to which they bond to form a 5- or 6-membered saturated heterocyclic group which may be intervened or not with a nitrogen

10 atom, an oxygen atom or a sulfur atom, wherein said heterocyclic group may optionally be substituted by a lower alkyl group or a lower alkanoyl group), a group of the formula:  $-E-(CO)_lNR^6R^7$  (wherein l is the same as defined above, E

15 is a lower alkylene group,  $R^6$  and  $R^7$  are the same or different and are hydrogen atom, a lower alkyl group, an amino-substituted lower alkyl group which may optionally have a lower alkyl substituent, or a lower alkanoyl group, or  $R^6$  and  $R^7$  may combine together with the nitrogen atom to which they bond to form a 5- or 6-membered saturated heterocyclic group which may be intervened or not with a nitrogen atom, an oxygen atom or a sulfur atom,

20 wherein said heterocyclic group may optionally be substituted by a lower alkyl group, a lower alkanoyl group or a lower alkoxycarbonyl group), a lower alkanoyloxy-substituted lower alkyl group, a lower alkoxycarbonyl-substituted lower alkyl group, an amino which may optionally be substituted by a lower alkyl group or a cycloalkyl group, a carboxy-substituted lower alkyl group, a lower alkylsulfonyloxy-substituted lower alkyl group, a phthalimide-substituted

25 lower alkyl group, an imidazolyl-substituted lower alkyl group, a 1,2,4-triazolyl-substituted lower alkyl group, an amino-substituted lower alkanoyloxy group which may optionally have a lower alkyl substituent, or an imidazolyl-substituted lower alkoxy group,

$R^3$  is hydrogen atom, a lower alkoxy group or a hydroxy-substituted lower

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alkyl group,

B<sub>1</sub> and B<sub>2</sub> are each methylene group or a group of the formula: -NR<sup>8</sup>-

(wherein R<sup>8</sup> is hydrogen atom or a lower alkyl group),

A is a 5- or 6-membered unsaturated heterocyclic residue having 1 to 2  
5 heteroatoms selected from an oxygen atom, a nitrogen atom and a sulfur atom,  
and

R is a group of the formula: -NHR<sup>A</sup> or a group of the formula:



wherein R<sup>A</sup> is a group of the formula:



[wherein m is an integer of 1 to 3, R<sup>18</sup> is hydrogen atom, a lower alkyl group, a lower alkoxy group, a halogen atom, nitro group, a lower alkoxy carbonyl group, a carboxy group, a lower alkoxy carbonyl-substituted lower alkoxy group, a hydroxy-substituted lower alkoxy group, a carboxy-substituted lower alkoxy  
20 group, a lower alkylsulfonyloxy-substituted lower alkoxy group, a phthalimide-substituted lower alkoxy group, or a group of the formula: -O-E-(CO)<sub>l</sub>NR<sup>19</sup>R<sup>20</sup>  
(wherein E and l are the same as defined above, R<sup>19</sup> and R<sup>20</sup> are the same or different and are hydrogen atom or a lower alkyl group, or R<sup>19</sup> and R<sup>20</sup> may combine together with the nitrogen atom to which they bond to form a 5- or 6-  
25 membered saturated heterocyclic group which may be intervened or not with a nitrogen atom or an oxygen atom, wherein said heterocyclic group may optionally be substituted by a lower alkyl group, or an amino group which may optionally be substituted by a lower alkanoyl group)], thienylcarbonyl group, a cycloalkylcarbonyl group or a phenyl-lower alkanoyl group which may

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optionally have a lower alkyl substituent on the phenyl ring,  
or a salt thereof.

The compounds of the formula (1) of the present invention and salts thereof show excellent vasopressin antagonistic activities, for examples,  
5 vasodilating activity, hypotensive activity, activity for inhibiting saccharide release in liver, activity for inhibiting growth of mesangium cells, water diuretic activity, platelet agglutination inhibitory activity, inhibitory activity for vomiting, and hence, they are useful as vasodilators, hypotensive agents, water diuretics, platelet agglutination inhibitor, etc., and are used in the prophylaxis or  
10 treatment of hypertension, edema, ascites, heart failure, renal function disorder, vasopressin parasecretion syndrome (SIADH), hepatocirrhosis, hyponatremia, hypokalemia, diabetic, circulation disorder, motion sickness, and the like. In addition, the compounds of the present invention and salts thereof show oxytocin antagonistic activities, for example, inhibitory effect on uterine smooth  
15 muscle constriction, inhibitory effect on milk secretion, inhibitory effect on synthesis and secretion of prostaglandin, and vasodilation activity, and hence, are useful in the protection or treatment of oxytocin-associated diseases, especially premature delivery, dysmenorrhea, endometritis, or in stopping labor preparatory to Caesarian delivery. Besides, the compounds of the present  
20 invention and salts thereof are characteristic in less side effects, and in prolonged action for a long time in living body.

Each group in the above formula (1) specifically includes the following groups.

The "lower alkoxy group" includes a straight chain or branched chain  
25 alkoxy group having 1 to 6 carbon atoms, for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, pentyloxy, hexyloxy, and the like.

The "lower alkyl group" includes a straight chain or branched chain alkyl group having 1 to 6 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl, and the like.

30 The "halogen atom" includes fluorine atom, chlorine atom, bromine atom, and iodine atom.

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The "lower alkylene group" includes a straight chain or branched chain alkylene group having 1 to 6 carbon atoms, for example, methylene, ethylene, trimethylene, 2-methyltrimethylene, 2,2-dimethyltrimethylene, 1-methyltrimethylene, methylmethylenes, ethylmethylenes, tetramethylene, pentamethylene, hexamethylene, and the like.

The "hydroxy-substituted lower alkoxy group" includes a straight chain or branched chain alkoxy group having 1 to 6 carbon atoms which is substituted by 1 to 3 hydroxy groups, for example, hydroxymethoxy, 2-hydroxyethoxy, 1-hydroxyethoxy, 3-hydroxypropoxy, 2,3-dihydroxyethoxy, 4-hydroxybutoxy, 3,4-dihydroxybutoxy, 1,1-dimethyl-2-hydroxyethoxy, 5-hydroxypentyl-oxy, 6-hydroxyhexyloxy, 2-methyl-3-hydroxypropoxy, 2,3,4-trihydroxybutoxy, and the like,

The "lower alkanoyl group" includes a straight chain or branched chain alkanoyl group having 1 to 6 carbon atoms, for example, formyl, acetyl, propionyl, butyryl, isobutyryl, pentanoyl, t-butylcarbonyl, hexanoyl, and the like.

The "carboxy-substituted lower alkyl group" includes a carboxyalkyl group wherein the alkyl moiety is a straight chain or branched chain alkyl group having 1 to 6 carbon atoms, for example, carboxymethyl, 2-carboxylethyl, 1-carboxyethyl, 3-carboxypropyl, 4-carboxybutyl, 5-carboxypentyl, 6-carboxyhexyl, 1,1-dimethyl-2-carboxyethyl, 2-methyl-3-carboxypropyl, and the like.

The "5- or 6-membered saturated heterocyclic group which is formed by combining the groups  $R^4$  and  $R^5$ , or the groups of  $R^6$  and  $R^7$  with the nitrogen atom to which they bond, which may be intervened or not with nitrogen atom, oxygen atom or sulfur atom" includes pyrrolidinyl, piperidinyl, piperazinyl, morpholino, thiomorpholino, and the like.

The "above mentioned heterocyclic group which is substituted by a lower alkyl group or a lower alkanoyl group" includes the above mentioned heterocyclic groups which are substituted by 1 to 3 groups selected from a straight chain or branched chain alkyl group having 1 to 6 carbon atoms and a straight chain or branched chain alkanoyl group having 1 to 6 carbon atoms, for example, 4-methylpiperazinyl, 3,4-dimethylpiperazinyl, 3-ethylpyrrolidinyl, 2-

propylpyrrolidinyl, 3,4,5-trimethylpiperidinyl, 4-butylpiperidinyl, 3-pentyl-morpholino, 3-methylthiomorpholino, 4-hexylpiperazinyl, 4-acetylpiperazinyl, 4-formyl-3-methylpiperazinyl, 3-propionylpyrrolidinyl, 2-butyrylpyrrolidinyl, 4-pentanoylpiperidinyl, 3-hexanoylmorpholino, 3,4,5-triacetylpiperidinyl, and the like.

The "above mentioned heterocyclic groups substituted by a lower alkyl group, a lower alkanoyl group or a lower alkoxy carbonyl group" includes the above mentioned heterocyclic groups substituted by 1 to 3 groups selected from a straight chain or branched chain alkyl group having 1 to 6 carbon atoms, a straight chain or branched chain alkanoyl group having 1 to 6 carbon atoms and a straight chain or branched chain alkoxy carbonyl group having 1 to 6 carbon atoms in the alkoxy moiety, for example, 4-methylpiperazinyl, 3,4-dimethylpiperazinyl, 3-ethylpyrrolidinyl, 2-propylpyrrolidinyl, 3,4,5-trimethylpiperidinyl, 4-butylpiperidinyl, 3-pentylmorpholino, 3-methylthiomorpholino, 4-hexylpiperazinyl, 4-acetylpiperazinyl, 4-formyl-3-methylpiperazinyl, 3-propionylpyrrolidinyl, 2-butyrylpyrrolidinyl, 4-pentanoylpiperidinyl, 3-hexanoylmorpholino, 3,4,5-triacetylpiperidinyl, 4-t-butoxycarbonylpiperazinyl, 3-methoxycarbonylpyrrolidinyl, 2-ethoxycarbonylpyrrolidinyl, 4-propoxycarbonylpiperidinyl, 3-pentyloxycarbonylmorpholino, 3-hexyloxycarbonylpiperidinyl, 3,5-dimethyl-4-t-butoxycarbonylpiperazinyl, 3-acetyl-4-t-butoxycarbonylpiperazinyl, and the like.

The "5- or 6-membered unsaturated heterocyclic residue having 1 to 2 heteroatoms selected from oxygen atom, nitrogen atom and sulfur atom" includes imidazolyl, pyrrolyl, imidazoliny, pyridyl, primidyl, oxazolyl, pyrazolyl, pyrazoliny, thiazolyl, thiazoliny, thienyl, furyl, pyranyl, isothiazolyl, isoxazolyl, pyrazinyl, pyridazinyl, pyrroliny, and the like.

The "cycloalkylcarbonyl group" includes a cycloalkylcarbonyl group having 3 to 8 carbon atoms in the cycloalkyl moiety, for example, cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl, cycloheptylcarbonyl, cyclooctylcarbonyl, and the like.

The "phenyl-lower alkanoyl wherein the phenyl moiety may



optionally have a lower alkyl substituent" includes phenylalkanoyl groups wherein the phenyl ring may optionally have 1 to 3 substituents of a straight chain or branched chain alkyl group having 1 to 6 carbon atoms and the alkanoyl moiety is a straight chain or branched chain alkanoyl group having 2  
5 to 6 carbon atoms, for example, phenylacetyl, 3-phenylpropionyl, 2-phenylpropionyl, 4-phenylbutyryl, 2,2-dimethyl-3-phenylpropionyl, 5-phenylpentanoyl, 6-phenylhexanoyl, (2-methylphenyl)acetyl, (3-methylphenyl)acetyl, (4-methylphenyl)acetyl, 2-(2-ethylphenyl)propionyl, 3-(3-isopropylphenyl)propionyl, 4-(3-butylphenyl)butyryl, 2,2-dimethyl-3-(4-pentylphenyl)propionyl, 5-(4-hexylphenyl)pentanoyl, 6-(3,4-dimethylphenyl)hexanoyl, (3,4,5-trimethylphenyl)-  
10 acetyl, and the like.

The "hydroxy-substituted lower alkyl group" includes a straight chain or branched chain alkyl group having 1 to 6 carbon atoms which has 1 to 3 hydroxy substituents, for example, hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl, 3-hydroxypropyl, 2,3-dihydroxyethyl, 4-hydroxybutyl, 3,4-dihydroxybutyl,  
15 1,1-dimethyl-2-hydroxyethyl, 5-hydroxypentyl, 6-hydroxyhexyl, 2-methyl-3-hydroxypropyl, 2,3,4-trihydroxybutyl, and the like.

The "lower alkylidene group" includes a straight chain or branched chain alkylidene group having 1 to 6 carbon atoms, for example, methylenidene, ethylenidene, propylenidene, isopropylenidene, butylenidene, pentylenidene, hexylenidene,  
20 and the like.

The "lower alkoxycarbonyl-substituted lower alkoxy group" includes a straight chain or branched chain alkoxy group having 1 to 6 carbon atoms which is substituted by a straight chain or branched chain alkoxycarbonyl group having 1 to 6 carbon atoms in the alkoxy moiety, for example,  
25 methoxycarbonylmethoxy, 3-methoxycarbonylpropoxy, ethoxycarbonylmethoxy, 3-ethoxycarbonylpropoxy, 4-ethoxycarbonylbutoxy, 5-isopropoxycarbonylpentyloxy, 6-propoxycarbonylhexyloxy, 1,1-dimethyl-2-butoxycarbonylethoxy, 2-methyl-3-t-butoxycarbonylpropoxy, 2-pentyloxycarbonylethoxy, hexyloxycarbonylmethoxy, and the like.  
30

The "carboxy-substituted lower alkoxy group" includes a carboxy-

alkoxy group wherein the alkoxy moiety is a straight chain or branched chain alkoxy group having 1 to 6 carbon atoms, for example, carboxymethoxy, 2-carboxyethoxy, 1-carboxyethoxy, 3-carboxypropoxy, 4-carboxybutoxy, 5-carboxypentyloxy, 6-carboxyhexyloxy, 1,1-dimethyl-2-carboxyethoxy, 2-methyl-3-carboxypropoxy, and the like.

The "lower alkylsulfonyloxy-substituted lower alkoxy group" includes an alkylsulfonyloxyalkoxy group wherein the alkylsulfonyloxy moiety is a straight chain or branched chain alkylsulfonyloxy group having 1 to 6 carbon atoms and the alkoxy moiety is a straight chain or branched chain alkoxy group having 1 to 6 carbon atoms, for example, methylsulfonyloxymethoxy, 3-methylsulfonyloxypropoxy, ethylsulfonyloxymethoxy, 3-ethylsulfonyloxypropoxy, 2-methylsulfonyloxyethoxy, 4-ethylsulfonyloxybutoxy, 5-isopropylsulfonyloxypropoxy, 6-propylsulfonyloxyhexyloxy, 1,1-dimethyl-2-butylsulfonyloxyethoxy, 2-methyl-3-t-butylsulfonyloxypropoxy, 2-pentylsulfonyloxyethoxy, hexylsulfonyloxymethoxy, and the like.

The "phthalimide-substituted lower alkoxy": group includes a phthalimide-substituted alkoxy group wherein the alkoxy moiety is a straight chain or branched chain alkoxy group having 1 to 6 carbon atoms, for example, phthalimidomethoxy, 2-phthalimidoethoxy, 1-phthalimidoethoxy, 3-phthalimidopropoxy, 4-phthalimidobutoxy, 5-phthalimidopentyloxy, 6-phthalimidohexyloxy, 1,1-dimethyl-2-phthalimidoethoxy, 2-methyl-3-phthalimidopropoxy, and the like.

The "lower alkoxycarbonyl-substituted lower alkyl group" includes an alkoxycarbonylalkyl group wherein the alkoxycarbonyl moiety is a straight chain or branched chain alkoxycarbonyl group having 1 to 6 carbon atoms in the alkoxy moiety and the alkyl moiety is a straight chain or branched chain alkyl group having 1 to 6 carbon atoms, for example, methoxycarbonylmethyl, 3-methoxycarbonylpropyl, ethoxycarbonylmethyl, 3-ethoxycarbonylpropyl, 4-ethoxycarbonylbutyl, 5-isopropoxycarbonylpentyl, 6-propoxycarbonylhexyl, 1,1-dimethyl-2-butoxycarbonylethyl, 2-methyl-3-t-butoxycarbonylpropyl, 2-pentyloxycarbonylethyl, hexyloxycarbonylmethyl, and the like.

The "amino which may optionally have 1 to 2 substituents of a lower alkyl group or a cycloalkyl group" includes an amino which may optionally be substituted by a straight chain or branched chain alkyl group having 1 to 6 carbon atoms or a cycloalkyl group having 3 to 8 carbon atoms, for example, amino, methylamino, ethylamino, propylamino, isopropylamino, butylamino, t-butylamino, pentylamino, hexylamino, dimethylamino, diethylamino, dipropylamino, dibutylamino, dipentylamino, dihexylamino, N-methyl-N-ethylamino, N-ethyl-N-propylamino, N-methyl-N-butylamino, N-methyl-N-hexylamino, cyclopropylamino, cyclobutylamino, cyclopentylamino, cyclohexylamino, cycloheptylamino, cyclooctylamino, dicyclopropylamino, dicyclobutylamino, dicyclopentylamino, dicyclohexylamino, dicycloheptylamino, dicyclooctylamino, N-methyl-N-cyclopropylamino, N-ethyl-N-cyclopropylamino, N-methyl-N-cyclopentylamino, N-ethyl-N-cyclohexylamino, and the like.

The "lower alkenyloxy group" includes a straight chain or branched chain alkenyloxy group having 2 to 6 carbon atoms, for example, vinyloxy, allyloxy, 2-butenyloxy, 3-butenyloxy, 1-methylallyloxy, 2-pentenylloxy, 2-hexenyloxy, and the like.

The "cycloalkyl group" includes cycloalkyl groups having 3 to 8 carbon atoms, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopentyl, cyclooctyl, and the like.

The "amino-substituted lower alkyl group which may optionally have a lower alkyl substituent" includes a straight chain or branched chain alkyl group having 1 to 6 carbon atoms which is substituted by an amino group optionally having 1 to 2 substituents of a straight chain or branched chain alkyl group having 1 to 6 carbon atoms, for example, aminomethyl, 2-aminoethyl, 1-aminoethyl, 3-aminopropyl, 4-aminobutyl, 5-aminopentyl, 6-aminohexyl, 1,1-dimethyl-2-aminoethyl, 2-methyl-3-aminopropyl, methylaminomethyl, 1-ethylaminoethyl, 2-propylaminoethyl, 3-isopropylaminopropyl, 4-butylaminobutyl, 5-pentylaminopentyl, 6-hexylaminohexyl, dimethylaminoethyl, 2-diethylaminoethyl, 2-dimethylaminoethyl, (N-ethyl-N-propylamino)methyl, 2-(N-methyl-N-hexylamino)ethyl, and the like.

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The "lower alkoxy carbonyl group" includes a straight chain or branched chain alkoxy carbonyl group having 1 to 6 carbon atoms in the alkoxy moiety, for example, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, t-butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl, and the like.

The "lower alkanoyloxy-substituted lower alkyl group" includes a straight chain or branched chain alkyl group having 1 to 6 carbon atoms which is substituted by a straight chain or branched chain alkanoyloxy group having 2 to 6 carbon atoms, for example, acetyloxymethyl, 2-acetyloxyethyl, 3-propionyloxypropyl, 4-butyryloxybutyl, 5-isobutyryloxypropyl, 1,1-dimethyl-2-pentanoyloxyethyl, 5-hexanoyloxypropyl, 6-acetyloxyhexyl, 2-methyl-3-acetyloxypropyl, and the like.

The "lower alkylsulfonyloxy-substituted lower alkyl group" includes a straight chain or branched chain alkyl group having 1 to 6 carbon atoms which is substituted by a straight chain or branched chain alkylsulfonyloxy group having 1 to 6 carbon atoms, for example, methylsulfonyloxymethyl, 3-methylsulfonyloxypropyl, ethylsulfonyloxymethyl, 3-ethylsulfonyloxypropyl, 2-methylsulfonyloxyethyl, 4-ethylsulfonyloxybutyl, 5-isopropylsulfonyloxypropyl, 6-propylsulfonyloxyhexyl, 1,1-dimethyl-2-butylsulfonyloxyethyl, 2-methyl-3-t-butylsulfonyloxypropyl, 2-pentylsulfonyloxyethyl, hexylsulfonyloxymethyl, and the like.

The "phthalimide-substituted lower alkyl group" includes a straight chain or branched chain alkyl group having 1 to 6 carbon atoms which is substituted by a phthalimide group, for example, phthalimidomethyl, 2-phthalimidoethyl, 1-phthalimidoethyl, 3-phthalimidopropyl, 4-phthalimidobutyl, 5-phthalimidopentyl, 6-phthalimidoethyl, 1,1-dimethyl-2-phthalimidoethyl, 2-methyl-3-phthalimidopropyl, and the like.

The "imidazolyl-substituted lower alkyl group" includes a straight chain or branched chain alkyl group having 1 to 6 carbon atoms which is substituted by an imidazolyl group, for example, (1-imidazolyl)methyl, 2-(1-imidazolyl)ethyl, 1-(2-imidazolyl)ethyl, 3-(4-imidazolyl)propyl, 4-(5-imidazolyl)-

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butyl, 5-(1-imidazolyl)pentyl, 6-(2-imidazolyl)hexyl, 1,1-dimethyl-2-(1-imidazolyl)ethyl, 2-methyl-3-(1-imidazolyl)propyl, and the like.

5 The "1,2,4-triazolyl-substituted lower alkyl group" includes a straight chain or branched chain alkyl group having 1 to 6 carbon atoms which is substituted by a 1,2,4-triazolyl group, for example, (1,2,4-triazol-1-yl)methyl, 2-(1,2,4-triazol-1-yl)ethyl, 1-(1,2,4-triazol-1-yl)ethyl, 3-(1,2,4-triazol-3-yl)propyl, 4-(1,2,4-triazol-5-yl)butyl, 5-(1,2,4-triazol-1-yl)pentyl, 6-(1,2,4-triazol-3-yl)hexyl, 1,1-dimethyl-2-(1,2,4-triazol-5-yl)ethyl, 2-methyl-3-(1,2,4-triazol-1-yl)propyl, and the like.

10 The "imidazolyl-substituted lower alkoxy group" includes a straight chain or branched chain alkoxy group having 1 to 6 carbon atoms which is substituted by an imidazolyl group, for example, (1-imidazolyl)methoxy, 2-(1-imidazolyl)ethoxy, 1-(2-imidazolyl)ethoxy, 3-(4-imidazolyl)propoxy, 4-(5-imidazolyl)butoxy, 5-(1-imidazolyl)pentyloxy, 6-(2-imidazolyl)hexyloxy, 1,1-dimethyl-2-(1-imidazolyl)ethoxy, 2-methyl-3-(1-imidazolyl)propoxy, and the like.

15 The "amino-substituted lower alkanoyloxy group which may optionally have a lower alkyl substituent" includes a straight chain or branched chain alkanoyloxy group having 2 to 6 carbon atoms which is substituted by an amino group optionally being substituted by 1 to 2 straight chain or branched chain alkyl groups having 1 to 6 carbon atoms, for example, 2-aminoacetyloxy, 3-aminopropionyloxy, 2-aminopropionyloxy, 4-aminobutyryloxy, 5-amino-pentanoyloxy, 6-aminohexanoyloxy, 2,2-dimethyl-3-aminopropionyloxy, 2-methyl-3-aminopropionyloxy, 2-methylaminoacetyloxy, 2-ethylamino-propionyloxy, 3-propylaminopropionyloxy, 3-isopropylaminopropionyloxy, 4-butylaminobutyryloxy, 5-pentylaminopentanoyloxy, 6-hexylaminohexanoyloxy, 2-dimethylaminoacetyloxy, 2-diethylaminoacetyloxy, 2-(N-ethyl-N-propylamino)-acetyloxy, 3-(N-methyl-N-hexylamino)propionyloxy, and the like.

25 The "an amino group which may optionally have a lower alkanoyl substituent" includes an amino group which may optionally have a substituent of a straight chain or branched chain alkanoyl group having 1 to 6 carbon atoms, for example, amino, acetylamino, propionylamino, isopropionylamino,

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butyrylamino, pentanoylamino, hexanoylamino, formylamino, and the like.

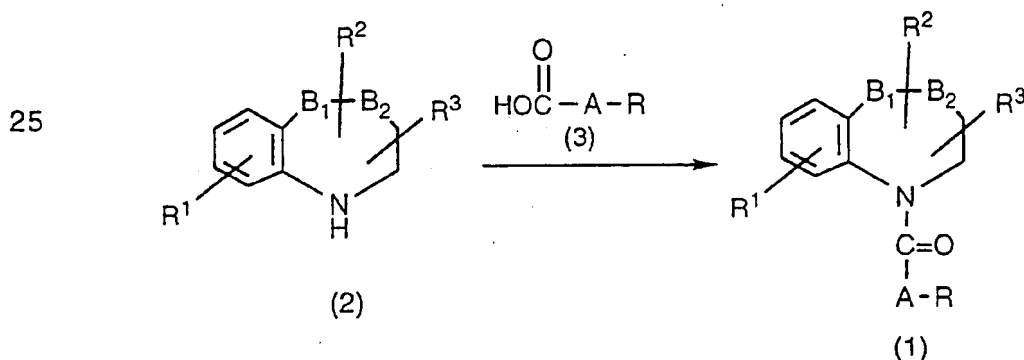
The "5- or 6-membered saturated heterocyclic group which is formed by combining the groups R<sup>19</sup> and R<sup>20</sup> with the nitrogen atom to which they bond, which may be intervened or not with nitrogen atom or oxygen atom"

5 includes, for example, pyrrolidinyl, piperidinyl, piperazinyl, morpholino, and the like.

The "above mentioned heterocyclic groups which are substituted by an amino group optionally being substituted by a lower alkyl group or a lower alkanoyl group" includes, for example, the above mentioned heterocyclic  
 10 groups which are substituted by 1 to 3 amino groups optionally being substituted by a straight chain or branched chain alkyl group having 1 to 6 carbon atoms, or a straight chain or branched chain alkanoyl group having 1 to 6 carbon atoms, for example, 4-methylpiperazinyl, 3,4-dimethylpiperazinyl, 3-ethylpyrrolidinyl, 2-propylpyrrolidinyl, 3,4,5-trimethylpiperidinyl, 4-butyl-  
 15 piperidinyl, 3-pentylmorpholino, 3-methyl-4-acetylamino piperidinyl, 4-hexylpiperazinyl, 4-acetylamino piperidinyl, 4-aminopiperidinyl, 2-propionyl-aminopiperazinyl, 2-isopropionylaminopyrrolidinyl, 3-butyrylamino morpholino, 4-methyl-3-acetylamino piperazinyl, 3-pentanoylamino piperazinyl, 4-hexanoyl-aminopiperidinyl, and the like.

20 The benzoheterocyclic compounds of the present invention can be prepared by the following processes.

#### Reaction Scheme-1



wherein R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, A, B<sub>1</sub> and B<sub>2</sub> are the same as defined above.

The process of Reaction Scheme-1 is carried out by reacting a benzoheterocyclic compound (2) and a carboxylic acid compound (3) by the conventional amino bond producing reaction. The amido bond producing  
5 reaction can be carried out under the conditions for the conventional amino bond producing reaction, for example,

(a) a mixed acid anhydride process, i.e. a process of reacting the carboxylic acid compound (3) with an alkyl halocarbonate ester to form a mixed acid anhydride and reacting the resultant with the amine compound (2),

10 (b) an activated ester process, i.e. a process of converting the carboxylic acid compound (3) into an activated ester such as p-nitrophenyl ester, N-hydroxysuccinimide ester, 1-hydroxybenzotriazole ester, etc., and reacting the resultant with the amine compound (2),

(c) a carbodiimide process, i.e. a process of condensing the carboxylic acid compound (3) and the amine compound (2) in the presence of an  
15 activating agent such as dicyclohexylcarbodiimide, carbonyldiimidazole, etc.,

(d) other processes, i.e. a process of converting the carboxylic acid compound (3) into a carboxylic anhydride by treating it with a dehydrating agent such as acetic anhydride, and reacting the resultant with the amine  
20 compound (2); a process of reacting an ester of the carboxylic acid compound (3) with a lower alcohol and the amine compound (2) at a high temperature under high pressure; a process of reacting an acid halide compound of the carboxylic acid compound (3), i.e. a carboxylic acid halide, with the amine compound (2), and the like.

25 The mixed acid anhydride used in the above mixed acid anhydride process (a) is obtained by the know Schotten-Baumann reaction, and the reaction product is used without isolating from the reaction mixture for the reaction with the amine compound (2) to give the desired compound (1) of the present invention. The Schotten-Baumann reaction is usually carried out in the  
30 presence of a basic compound. The basic compound is any conventional

compounds used for the Schotten-Baumann reaction and includes, for example, organic basic compounds such as triethylamine, trimethylamine, pyridine, dimethylaniline, N-methylmorpholine, 1,5-diazabicyclo[4.3.0]nonene-5 (DBN), 1,8-diazabicyclo[5.4.0]undecene-7 (DBU), 1,4-diazabicyclo[2.2.2]-octane (DABCO), and inorganic basic compounds such as potassium carbonate, sodium carbonate, potassium hydrogen carbonate, sodium hydrogen carbonate, etc. The reaction is usually carried out at a temperature from about -20°C to about 100°C, preferably at 0°C to about 50°C, for about 5 minutes to about 10 hours, preferably for 5 minutes to about 2 hours.

10           The reaction between the mixed acid anhydride thus obtained and the amine compound (2) is usually carried out at -20°C to about 150°C, preferably at 10°C to about 50°C, for 5 minutes to about 10 hours, preferably for 5 minutes to 5 hours. The mixed acid anhydride process is usually carried out in a solvent. The solvent may be any conventional solvents which are usually

15           used in the mixed acid anhydride process and includes, for example, halogenated hydrocarbons (e.g. chloroform, dichloromethane, dichloroethane, etc.), aromatic hydrocarbons (e.g. benzene, toluene, xylene, etc.), ethers (e.g. diethyl ether, diisopropyl ether, tetrahydrofuran, dimethoxyethane, etc.), esters (e.g. methyl acetate, ethyl acetate, etc.), aprotic polar solvents (e.g. N,N-

20           dimethylformamide, dimethylsulfoxide, acetonitrile, hexamethylphosphoric triamide, etc.), or a mixture of these solvents. The alkyl halocarbonate ester used in the mixed acid anhydride process includes, for example, methyl chloroformate, methyl bromoformate, ethyl chloroformate, ethyl bromoformate, isobutyl chloroformate, and the like. In said process, the carboxylic acid

25           compound (3), the alkyl halocarbonate ester and the amine compound (2) are usually used in each equimolar amount, but preferably, the alkyl halocarbonate ester and the carboxylic acid compound (3) are used each in an amount of about 1 to 1.5 mole to 1 mole of the amine compound (2).

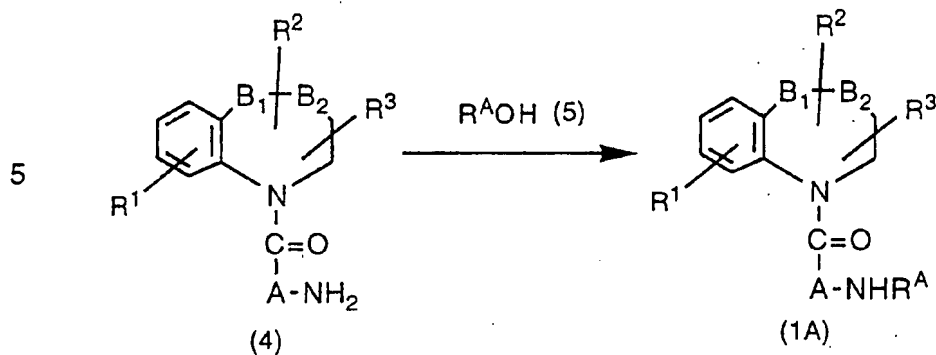
30           Among the above other processes (d), in case of the process of reacting the carboxylic acid halide with the amine compound (2), the reaction is usually carried out in the presence of a basic compound in an appropriate



solvent. The basic compound is any conventional compounds and includes, for example, in addition to the basic compounds used for Schotten-Baumann reaction, sodium hydroxide, potassium hydroxide, sodium hydride, potassium hydride, and the like. The solvent includes, for example, in addition to the  
5 solvents used in the mixed acid anhydride process, alcohols (e.g. methanol, ethanol, propanol, butanol, 3-methoxy-1-butanol, ethylcellosolve, methylcellosolve, etc.), pyridine, acetone, water, and the like. The amount of the amine compound (2) and the carboxylic acid halide is not critical, but the carboxylic acid halide is usually used at least in equimolar amount, preferably  
10 about 1 to 5 moles to 1 mole of the amine compound (2). The reaction is usually carried out at a temperature from about -20°C to about 180°C, preferably at 0°C to about 150°C, for about 5 minutes to about 30 hours.

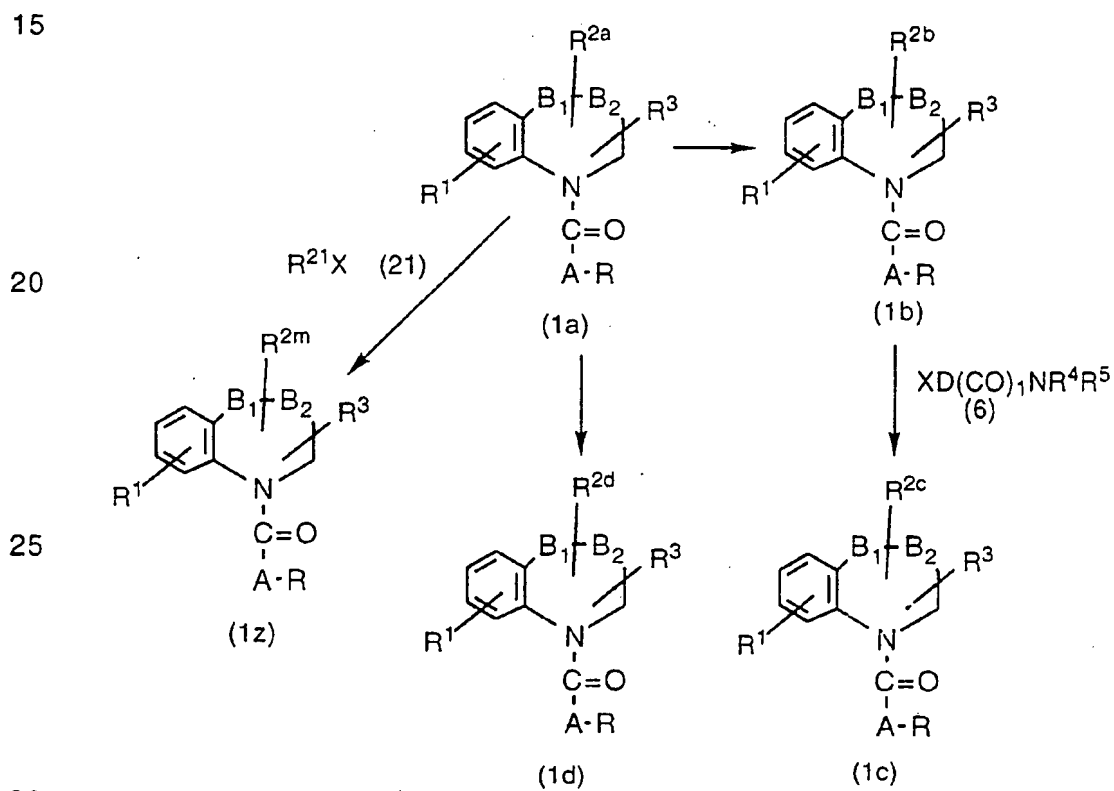
The amido bond producing reaction in Reaction Scheme-1 may also be carried out by reacting the carboxylic acid compound (3) and the amine  
15 compound (2) in the presence of a condensing agent such as phosphorus compounds (e.g. triphenylphosphine, diphenylphosphonyl chloride, phenyl-N-phenylphosphoramidate chloridate, diethyl chlorophosphate, diethyl cyanophosphate, diphenylphosphoric azide, bis(2-oxo-3-oxazolidinyl)phosphinic chloride, etc. The reaction is usually carried out in the presence of the solvent  
20 and the basic compound as used in the above reaction of the carboxylic acid halide and the amide compound (2) at a temperature from -20°C to 150°C, preferably from 0°C to about 100°C, for about 5 minutes to about 30 hours. The condensing agent and the carboxylic acid compound (3) are used at least in equimolar amount, preferably about 1 to 2 moles, to 1 mole of the amine  
25 compound (2).

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Reaction Scheme-2

10 wherein  $R^A$ ,  $R^1$ ,  $R^2$ ,  $R^3$ , A,  $B_1$  and  $B_2$  are the same as defined above.

The reaction of the compound (4) and the compound (5) is carried out in the same conditions as in the reaction of the compound (2) and the compound (3) in Reaction Scheme-1.

Reaction Scheme-3

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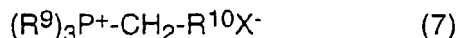
wherein R, R<sup>1</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, D, I, B<sub>1</sub>, A and B<sub>2</sub> are the same as defined above, R<sup>2a</sup> is oxo group, R<sup>2b</sup> is hydroxy group, R<sup>2c</sup> is a group of the formula:  
-O-D(CO)<sub>n</sub>NR<sup>4</sup>R<sup>5</sup> (D, I, R<sup>4</sup> and R<sup>5</sup> are the same as defined above), R<sup>2d</sup> is a lower alkylidene group, R<sup>2m</sup> is a lower alkoxy group or a lower alkenyloxy group, R<sup>21</sup> is a lower alkyl group or a lower alkenyl group, and X is a halogen atom.

The reaction of converting the compound (1a) into the compound (1b) is carried out by subjecting the compound (1a) to reduction reaction. The reduction reaction is preferably carried out by using a hydrogenation agent. The hydrogenation agent includes, for example, lithium aluminum hydride, sodium borohydride, sodium trimethoxyborohydride, lithium borohydride, diborane, and the like. The hydrogenation agent is used at least in an equimolar amount, preferably 1 mole to 15 moles, to 1 mole of the starting compound. The reduction reaction is usually carried out in an appropriate solvent such as water, lower alcohols (e.g. methanol, ethanol, isopropanol, t-butanol, etc.), ethers (e.g. tetrahydrofuran, diethyl ether, diisopropyl ether, ethylene glycol dimethyl ether, diglyme, etc.), or a mixture thereof, at a temperature from -60°C to 150°C, preferably at -30°C to 100°C, for about 10 minutes to about 15 hours. In case that lithium aluminum hydride or diborane is used as a reducing agent, it is preferable to use an anhydrous solvent such as tetrahydrofuran, diethyl ether, diisopropyl ether, diglyme, and the like.

The reaction between the compound (1b) and the compound (6) is usually carried out in an appropriate inert solvent in the presence or absence of a basic compound. The inert solvent includes, for example, aromatic hydrocarbons (e.g. benzene, toluene, xylene, etc.), ethers (e.g. tetrahydrofuran, dioxane, diethylene glycol dimethyl ether, etc.), halogenated hydrocarbons (e.g. dichloromethane, chloroform, carbon tetrachloride, etc.), lower alcohols (e.g. methanol, ethanol, isopropanol, butanol, t-butanol, etc.), acetic acid, ethyl acetate, acetone, acetonitrile, pyridine, dimethyl sulfoxide, dimethylformamide, hexamethylphosphoric triamide, or a mixture thereof. The basic compound

includes, for example, metal carbonates and metal hydrogen carbonates (e.g. sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogen carbonate, etc.), metal hydroxides (sodium hydroxide, potassium hydroxide, etc.), sodium hydride, potassium, sodium, sodium amide, metal alcoholates (e.g. sodium methylate, sodium ethylate, etc.), organic basic compounds (e.g. pyridine, N-ethyldiisopropylamine, dimethylaminopyridine, triethylamine, 1,5-diazabicyclo[4.3.0]nonene-5 (DBN), 1,8-diazabicyclo[5.4.0]-undecene-7 (DBU), 1,4-diazabicyclo[2.2.2]octane (DABCO), and the like. The amount of the compound (1b) and the compound (6) is not critical, but the compound (6) is used at least in an equimolar molar, preferably in an amount of 1 mole to 10 moles, to 1 mole of the compound (1b). The reaction is usually carried out at a temperature from 0°C to about 200°C, preferably 0°C to about 170°C, for about 30 minutes to about 30 hours. An alkali metal halide such as sodium iodide, potassium iodide, etc. may be added to this reaction system.

The reaction of converting the compound (1a) into the compound (1d) is carried out in an appropriate solvent in the presence of a phosphonium salt and a basic compound. The phosphonium salt includes, for example, a phosphorus compound of the following formula.



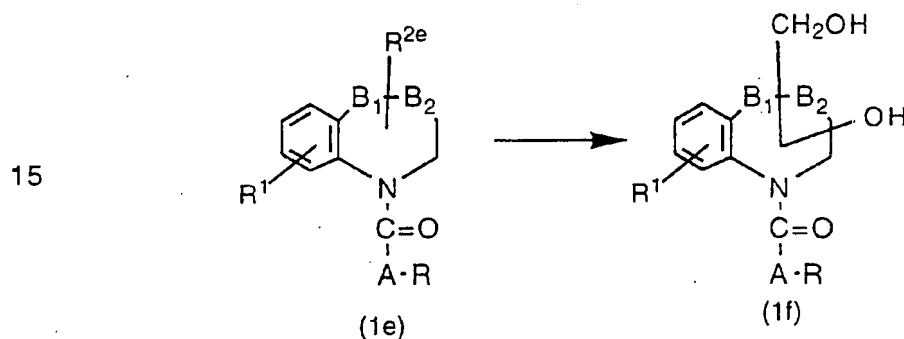
wherein  $R^9$  is phenyl group,  $R^{10}$  is hydrogen atom or a lower alkyl group, and X is the same as defined above. The basic compound includes, for example, inorganic bases such as sodium, potassium, sodium hydride, sodium amide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogen carbonate, etc., and organic bases such as metal alcoholates (e.g. sodium methylate, sodium ethylate, potassium t-butoxide, etc.), alkyl lithium, aryl lithium or lithium amide (e.g. methyl lithium, n-butyl lithium, phenyl lithium, lithium diisopropylamide, etc.), pyridine, piperidine, quinoline, triethylamine, N,N-dimethylaniline, and the like. The solvent may be any one which does not affect the reaction, and includes, for example, ethers (e.g. diethyl ether, dioxane, tetrahydrofuran, monoglyme, diglyme, etc.),

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aromatic hydrocarbons (e.g. benzene, toluene, xylene, etc.), aliphatic hydrocarbons (e.g. n-hexane, heptane, cyclohexane, etc.), aprotic polar solvents (e.g. pyridine, N,N-dimethylaniline, N,N-dimethylformamide, dimethyl sulfoxide, hexamethylphosphoric triamide, etc.), alcohols (e.g. methanol, ethanol, isopropanol, etc.), and the like. The reaction is usually carried out at a temperature from -80°C to 150°C, preferably at a temperature from -80 to about 120°C, for 0.5 to about 15 hours.

The reaction between the compound (1a) and the compound (21) can be carried out under the same conditions as those of the reaction between the compound (1b) and the compound (6).

#### Reaction Scheme-4



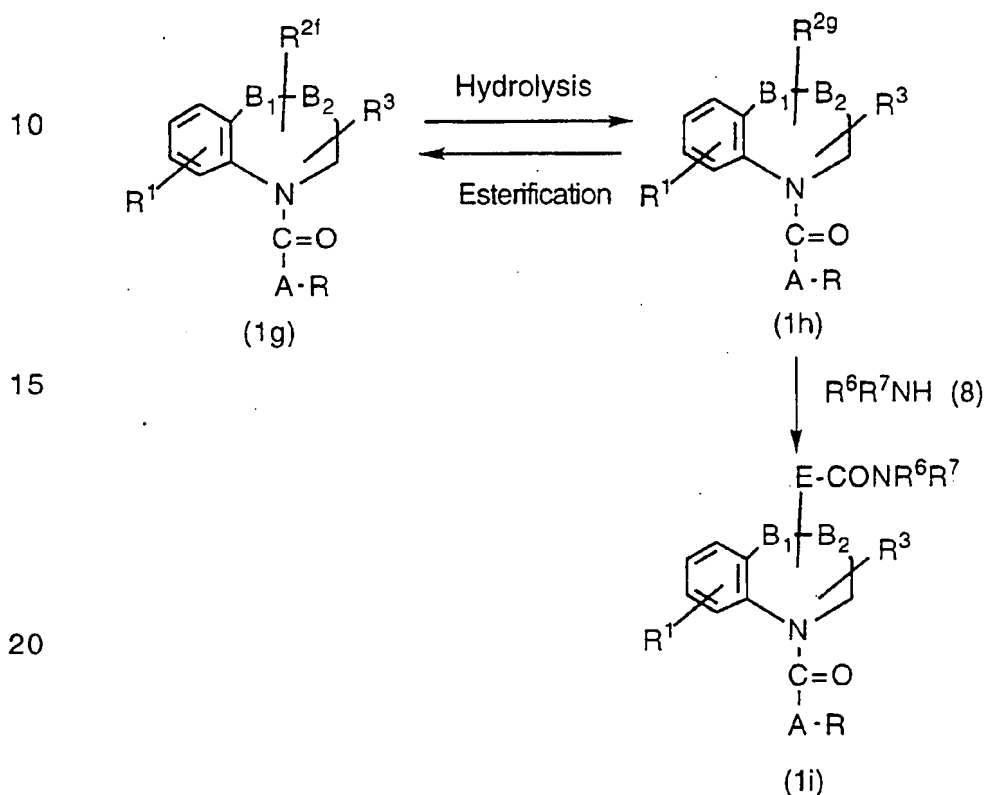
wherein R, R<sup>1</sup>, A, B<sup>1</sup> and B<sup>2</sup> are the same as defined above, and R<sup>2e</sup> is methylenide group.

The reaction of converting the compound (1e) into the compound (1f) is carried out by reacting with an oxidizing agent in the presence of a co-oxidizing agent in an appropriate solvent. The solvent used in the reaction with an oxidizing agent includes, for example, ethers (e.g. pyridine, dioxane, tetrahydrofuran, diethyl ether, etc.), aromatic hydrocarbons (e.g. benzene, toluene, xylene, etc.), halogenated hydrocarbons (e.g. dichloromethane, dichloroethane, chloroform, carbon tetrachloride, etc.), esters (e.g. ethyl acetate, etc.), water, alcohols (e.g. methanol, ethanol, isopropanol, t-butanol, etc.), or a mixture of these solvents. The co-oxidizing agent includes, N-oxides of organic amines such as pyridine N-oxide, N-ethyldiisopropylamine N-oxide, N-methylmorpholine N-oxide, trimethylamine N-oxide, triethylamine N-oxide,

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and the like. The oxidizing agent includes, for example, osmium tetroxide, and the like. The oxidizing agent is used at least in equimolar amount, preferably in an amount of 1 mole to 5 moles, to 1 mole of the starting compound. The reaction is carried out at a temperature from about -20°C to about 150°C, preferably at a temperature from room temperature to about 100°C, for 1 to about 10 hours.

Reaction Scheme-5



wherein  $R$ ,  $R^1$ ,  $R^3$ ,  $R^6$ ,  $R^7$ ,  $E$ ,  $B_1$ ,  $A$  and  $B_2$  are the same as defined above,  $R^{2f}$  is a lower alkoxycarbonyl-substituted lower alkyl group, and  $R^{2g}$  is a carboxy-substituted lower alkyl group.

The hydrolysis of the compound (1g) is carried out in the presence of an acid or a basic compound in an appropriate solvent or without a solvent. The solvent includes, for example, water, alcohols (e.g. methanol, ethanol, isopropanol, etc.), ketones (e.g. acetone, methyl ethyl ketone, etc.), ethers (e.g.

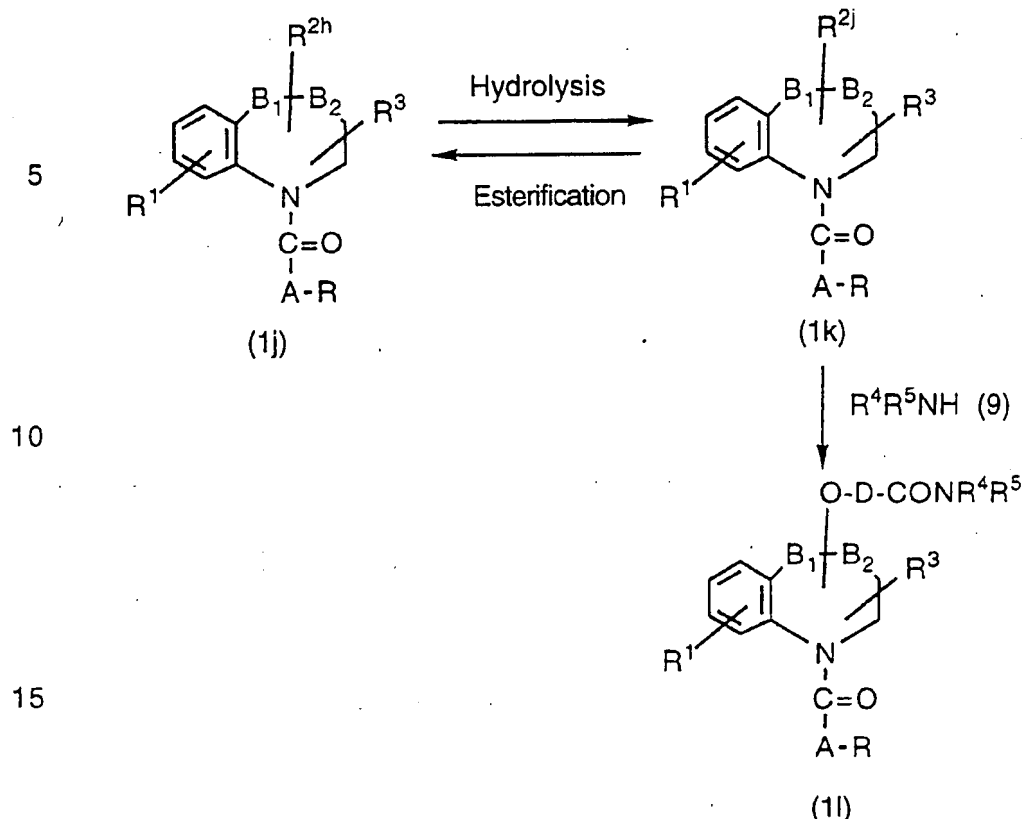
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dioxane, tetrahydrofuran, ethylene glycol dimethyl ether, etc.), fatty acids (e.g. acetic acid, formic acid, etc.), or a mixture of these solvents. The acid includes, for example, mineral acids (e.g. hydrochloric acid, sulfuric acid, hydrobromic acid, etc.) and organic acids (e.g. formic acid, acetic acid, aromatic sulfonic acid, etc.). The basic compound includes, for example, metal carbonates (e.g. sodium carbonate, potassium carbonate, etc.), metal hydroxides (e.g. sodium hydroxide, potassium hydroxide, calcium hydroxide, etc.), and the like. The reaction is usually carried out at a temperature from room temperature to about 200°C, preferably at a temperature from room temperature to about 150°C, for 10 minutes to about 25 hours.

The esterification of the compound (1h) is carried out by reacting the starting compound with an alcohol (e.g. methanol, ethanol, isopropanol, etc.) in the presence of a mineral acid (e.g. hydrochloric acid, sulfuric acid, etc.), or a halogenating agent (e.g. thionyl chloride, phosphorus oxychloride, phosphorus pentachloride, phosphorus trichloride) at a temperature from 0°C to 150°C, preferably at a temperature from 50°C to 100°C, for about 1 to about 10 hours.

The reaction between the compound (1h) and the compound (8) is carried out under the same conditions as those of the reaction between the compound (2) and the compound (3) in Reaction Scheme-1.

## Reaction Scheme-6



wherein  $R$ ,  $R^1$ ,  $R^3$ ,  $A$ ,  $B_1$ ,  $B_2$ ,  $R^4$ ,  $R^5$  and  $D$  are the same as defined above,  $R^{2h}$  is a lower alkoxy-carbonyl-substituted lower alkoxy group,  $R^{2i}$  is a carboxy-substituted lower alkoxy group.

20

The hydrolysis of the compound (1j) is carried out under the same conditions as those of the hydrolysis of the compound (1g) in Reaction Scheme-5.

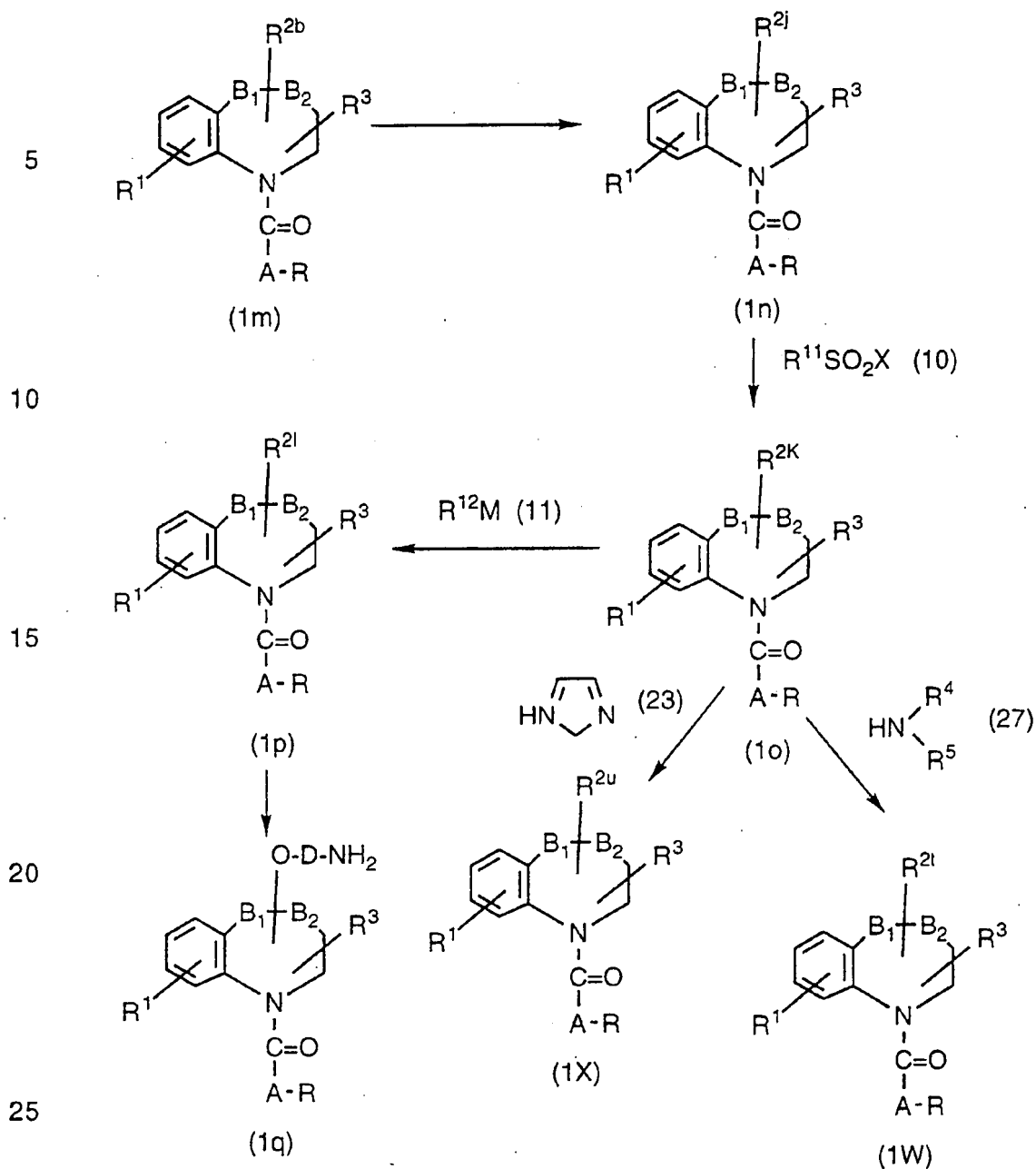
The esterification of the compound (1k) is carried out under the same conditions as those of the esterification of the compound (1h) in Reaction Scheme-5.

25

The reaction between the compound (1k) and the compound (9) is carried out under the same conditions as those of the reaction between the compound (2) and the compound (3) in Reaction Scheme-1.



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Reaction Scheme-7

wherein  $R$ ,  $R^1$ ,  $R^3$ ,  $R^{2h}$ ,  $R^4$ ,  $R^5$ ,  $A$ ,  $B_1$ ,  $B_2$ ,  $D$  and  $X$  are the same as defined above,  $R^{2j}$  is a hydroxy-substituted lower alkoxy group,  $R^{11}$  is a lower alkyl group,  $R^{2k}$  is a lower alkylsulfonyloxy-substituted lower alkoxy group,  $R^{2l}$  is a phthalimide-substituted lower alkoxy group,  $M$  is an alkali metal such as

potassium, sodium, etc.,  $R^{2t}$  is a group of the formula:  $-O-D-NR^4R^5$  (wherein D,  $R^4$  and  $R^5$  are the same as defined above), and  $R^{2u}$  is an imidazolyl-substituted lower alkoxy group.

5           The reaction of converting the compound (1m) into the compound (1n) is carried out under the same conditions as those of the reaction of converting the compound (1a) into the compound (1b) in Reaction Scheme-3.

          The reaction between the compound (1n) and the compound (10) is carried out under the same conditions as those of the reaction between the compound (1b) and the compound (6) in Reaction Scheme-3.

10           The reaction between the compound (1o) and the compound (11) is carried out under the same conditions as those of the reaction between the compound (1b) and the compound (6) in Reaction Scheme-3.

          The reaction of converting the compound (1p) into the compound (1q) is carried out by reacting the compound (1p) with hydrazine, or by  
15   hydrolysis of the compound (1p), in an appropriate solvent. The solvent used in the reaction with hydrazine includes, for example, the solvents used for the reaction between the compound (2) and the compound (3) in Reaction Scheme-1 as well as water. The reaction is usually carried out at a  
20   temperature from 0°C to about 120°C, preferably from 0°C to about 100°C, for 0.5 to about 5 hours. Hydrazine is used at least in equimolar amount, preferably in an amount of 1 mole to 5 moles, to 1 mole of the compound (1p).

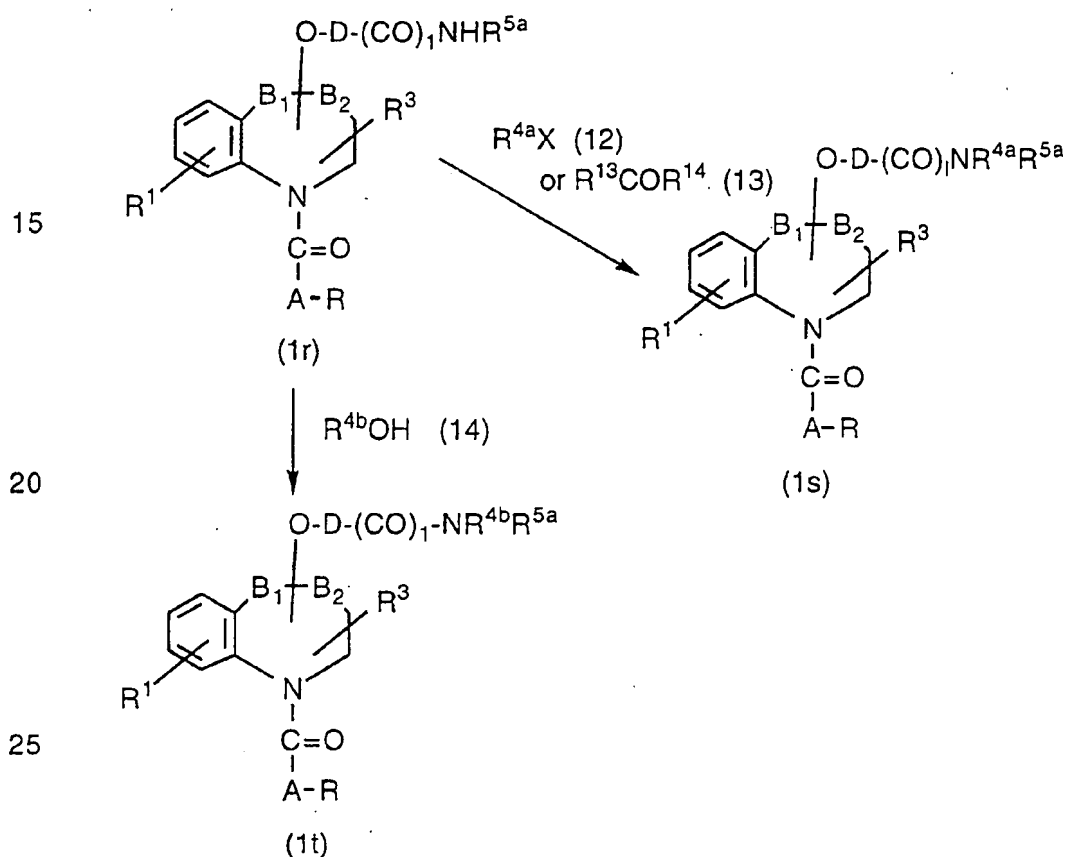
          The above hydrolysis is carried out in the presence of an acid or a basic compound in an appropriate solvent or without a solvent. The solvent includes, for example, water, alcohols (e.g. methanol, ethanol, isopropanol,  
25   etc.), ketones (e.g. acetone, methyl ethyl ketone, etc.), ethers (e.g. dioxane, tetrahydrofuran, ethylene glycol dimethyl ether, etc.), fatty acids (e.g. acetic acid, formic acid, etc.), or a mixture of these solvents. The acid includes, for example, mineral acids (e.g. hydrochloric acid, sulfuric acid, hydrobromic acid, etc.), and organic acids (e.g. formic acid, acetic acid, aromatic sulfonic acid,  
30   etc.). The basic compound includes, for example, metal carbonates (e.g.

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sodium carbonate, potassium carbonate, etc.), metal hydroxides (e.g. sodium hydroxide, potassium hydroxide, calcium hydroxide, etc.), and the like. The reaction is usually carried out at a temperature from room temperature to about 200°C, preferably at a temperature from room temperature to about 150°C, for 10 minutes to about 25 hours.

The reaction between the compound (1o) and the compound (27), and the reaction between the compound (1o) and the compound (23) can be carried out under the same conditions as those of the reaction between the compound (1b) and the compound (6) in Reaction Scheme-3.

#### Reaction Scheme-8



wherein  $\text{R}$ ,  $\text{R}^1$ ,  $\text{R}^3$ ,  $\text{A}$ ,  $\text{B}_1$ ,  $\text{B}_2$  and  $\text{X}$  are the same as defined above,  $\text{R}^{4a}$  is a lower alkyl group, a cycloalkyl group or an amino-substituted lower alkyl group which may optionally have a lower alkyl substituent,  $\text{R}^{13}$  and  $\text{R}^{14}$  are each

hydrogen atom or a lower alkyl group, R<sup>4b</sup> is a lower alkanoyl group, and R<sup>5a</sup> is hydrogen atom, a lower alkyl group, a lower alkanoyl group, a cycloalkyl group or an amino-substituted lower alkyl group which may optionally have a lower alkyl substituent.

5           The reaction between the compound (1r) and the compound (12) is carried out under the same conditions as those of the reaction between the compound (1b) and the compound (6) in Reaction Scheme-3.

          The reaction between the compound (1r) and the compound (13) is carried out in the presence of a reducing agent in an appropriate solvent or  
10   without a solvent. The solvent includes, for example, water, alcohols (e.g. methanol, ethanol, isopropanol, etc.), acetonitrile, formic acid, acetic acid, ethers (e.g. dioxane, diethyl ether, diglyme, tetrahydrofuran, etc.), aromatic hydrocarbons (e.g. benzene, toluene, xylene, etc.), or a mixture thereof. The reducing agent includes, for example, formic acid, alkali metal salts of fatty  
15   acids (e.g. sodium formate, etc.), hydrogenation agents (e.g. sodium borohydride, sodium cyanoborohydride, lithium aluminum hydride, etc.), catalytic reducing agents (e.g. palladium-black, palladium-carbon, platinum oxide, platinum black, Ranney nickel, etc.), and the like.

          When formic acid is used as a reducing agent, the reaction is usually  
20   carried out at a temperature from room temperature to about 200°C, preferably at about 50°C to about 150°C, for about one to about 10 hours. Formic acid is used in an excess amount to the compound (1r).

          When a hydrogenation agent is used, the reaction is usually carried out at a temperature from about -30°C to about 100°C, preferably about 0°C to  
25   about 70°C, for about 30 minutes to about 12 hours. The hydrogenation agent is used in an amount of 1 mole to 20 moles, preferably in an amount of 1 mole to 6 moles, to 1 mole of the compound (1r). Especially, when lithium aluminum hydride is used as a reducing agent, the solvent is preferably ethers (e.g. diethyl ether, dioxane, tetrahydrofuran, diglyme, etc.) or aromatic hydrocarbons  
30   (e.g. benzene, toluene, xylene, etc.).

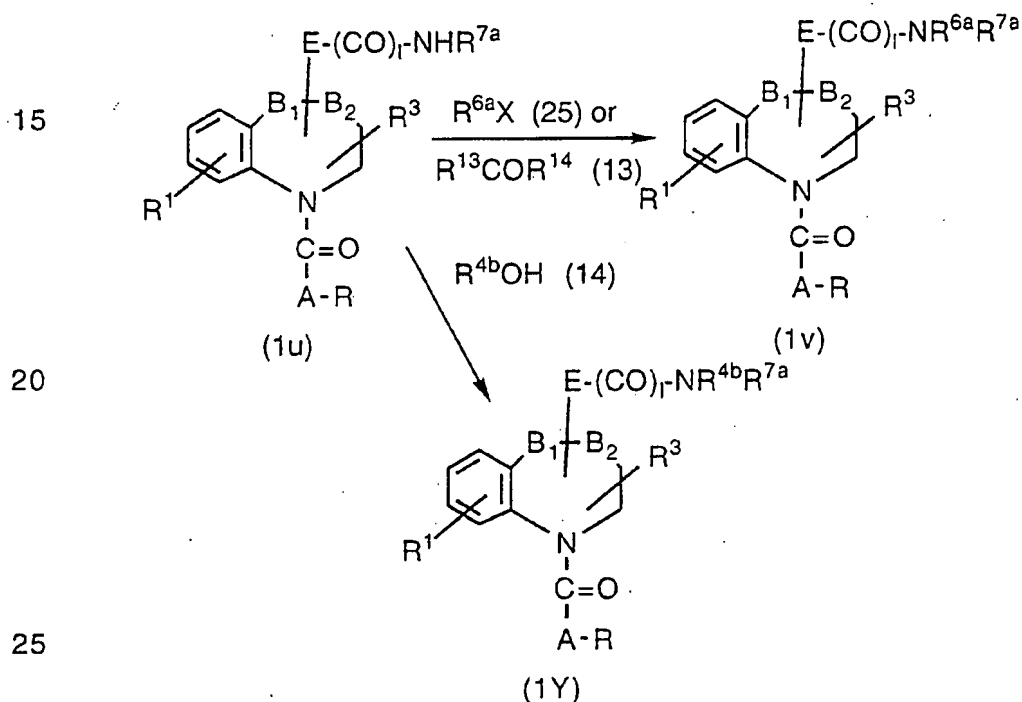
          Moreover, when a reducing agent is used, the reaction is usually

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carried out under atmospheric pressure to 20 atms of hydrogen, preferably, under atmospheric pressure to 10 atms of hydrogen, or in the presence of a hydrogen donor such as formic acid, ammonium formate, cyclohexene, hydrazine hydrate, etc., at -30°C to 100°C, preferably at 0°C to 60°C, for about one to 12 hours. The reducing agent is usually used in an amount of 0.1 to 40 % by weight, preferably 1 to 20 % by weight to the amount of the compound (1r). The compound (13) is usually used at least in equimolar amount, preferably in equimolar to excess amount, to the compound (1r).

The reaction between the compound (1r) and the compound (14) is carried out under the same conditions as those of the reaction between the compound (2) and the compound (3) in Reaction Scheme-1.

Reaction Scheme-9



wherein  $R$ ,  $R^1$ ,  $R^3$ ,  $A$ ,  $B_1$ ,  $B_2$ ,  $R^{13}$ ,  $R^{14}$ ,  $E$ ,  $R^{4b}$ ,  $l$  and  $X$  are the same as defined above,  $R^{6a}$  is a lower alkyl group or an amino-substituted lower alkyl group which may optionally have a lower alkyl substituent, and  $R^{7a}$  is hydrogen atom, a lower alkyl group, an amino-substituted lower alkyl group which may

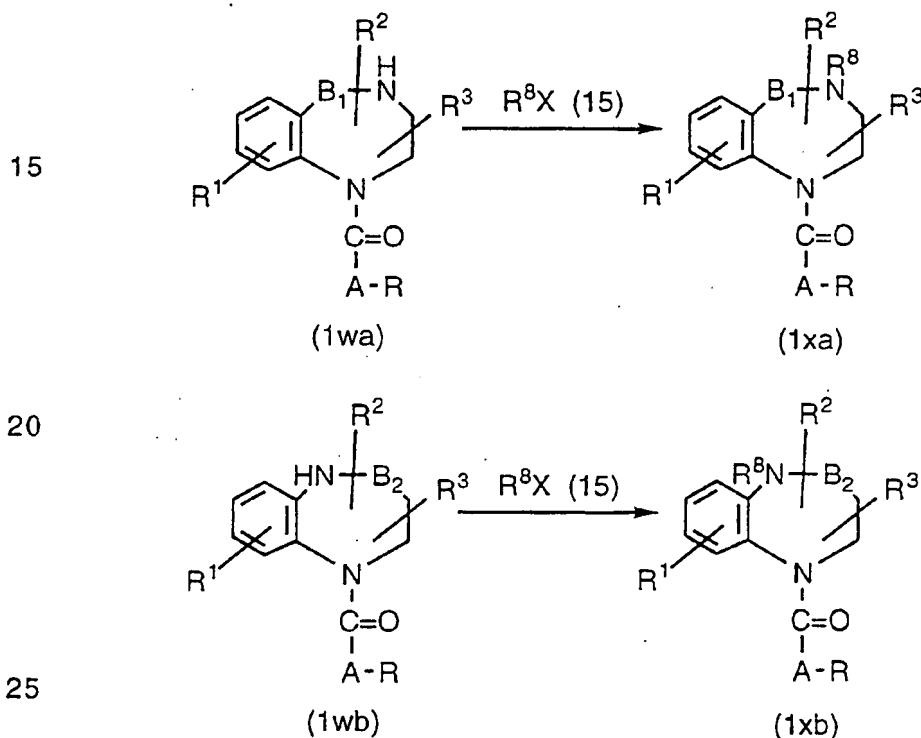
- 28 -

optionally have a lower alkyl substituent, or a lower alkanoyl group.

The reaction between the compound (1u) and the compound (25) is carried out under the same conditions as those of the reaction between the compound (1b) and the compound (6) in Reaction Scheme-3.

5 The reaction between the compound (1u) and the compound (13) is carried out under the same conditions as those of the reaction between the compound (1r) and the compound (13) in Reaction Scheme-8. The reaction between the compound (1u) and the compound (14) is carried out under the same conditions as those of the reaction between the compound (2) and the compound (3) in Reaction Scheme-1.

Reaction Scheme-10

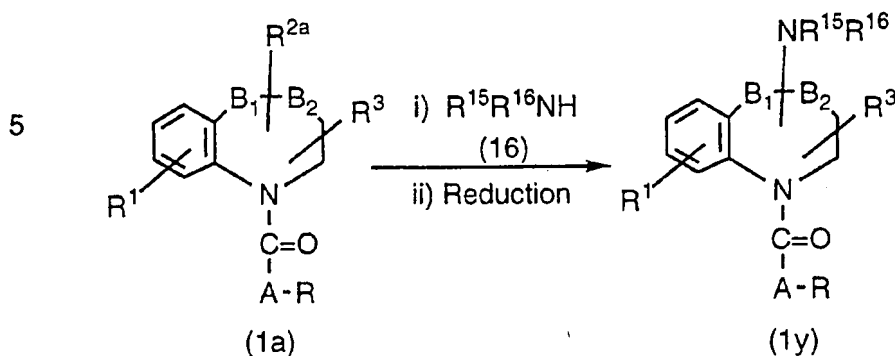


wherein  $R$ ,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $B_1$ ,  $B_2$ ,  $A$ ,  $R^8$  and  $X$  are the same as defined above.

The reaction between the compound (1wa) or the compound (1wb) and the compound (15) is carried out under the same conditions as those of the reaction between the compound (1b) and the compound (6) in Reaction

30

Scheme-3.

Reaction Scheme-11

The reaction of converting the compound (1a) into the compound

15 (1y) is carried out in the presence or absence of a dehydrating agent in an appropriate solvent or without a solvent. The solvent includes, for example, alcohols (e.g. methanol, ethanol, isopropanol; etc.), aromatic hydrocarbons (e.g. benzene, toluene, xylene, etc.), halogenated hydrocarbons (e.g. dichloromethane, dichloroethane, chloroform, carbon tetrachloride, etc.),

20 aprotic polar solvents (e.g. dimethylformamide, dimethylacetamide, N-methylpyrrolidone, etc.), or a mixture of these solvents. The dehydrating agent includes, for example, drying agents which are conventionally used for drying solvents (e.g. molecular sieve, etc.), mineral acids (e.g. hydrochloric acid, sulfuric acid, boron trifluoride, etc.), organic acids (e.g. p-toluenesulfonic acid, etc.), or a mixture thereof. The reaction is usually carried out at a temperature

25 from room temperature to 250°C, preferably at a temperature from about 50°C to about 200°C, for one to about 48 hours. The amount of the compound (16) is not critical, but it is used at least in equimolar amount, preferably 1 mole to excess amount, to 1 mole of the compound (1a). The dehydrating agent is

30 used in an excess amount when a drying agent is used, and when an acid is

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used as a dehydrating agent, it is used in a catalytic amount.

The subsequent reduction is carried out by various reduction reactions, for example, by catalytic hydrogenation in the presence of a catalyst in an appropriate solvent. The solvent includes, for example, water, acetic acid, 5 alcohols (e.g. methanol, ethanol, isopropanol, etc.), hydrocarbons (e.g. hexane, cyclohexane, etc.), ethers (e.g. diethylene glycol dimethyl ether, dioxane, tetrahydrofuran, diethyl ether, etc.), esters (e.g. ethyl acetate, methyl acetate, etc.), aprotic polar solvents (e.g. dimethylformamide, etc.), or a mixture of these solvents. The catalyst is, for example, palladium, palladium-black, palladium-carbon, 10 platinum, platinum oxide, copper chromite, Ranney nickel, and the like. The catalyst is usually used in an amount of 0.02 to 1 mole to 1 mole of the starting compound. The reaction is usually carried out at a temperature from -20°C to about 100°C, preferably at a temperature from 0°C to about 70°C, under a pressure of 1 atm to 10 atms of hydrogen, for 0.5 to 20 hours.

15 The above mentioned conditions for reduction can be employed in the present reduction, but the reduction using a hydrogenation agent is more preferable. The hydrogenation agent includes, for example, lithium aluminum hydride, sodium borohydride, diboran, etc., and is used at least in equimolar amount, preferably in an amount of 1 mole to 10 moles, to 1 mole of the 20 compound (1a). The reduction is carried out in an appropriate solvent such as water, lower alcohols (e.g. methanol, ethanol, isopropanol, etc.), ethers (e.g. tetrahydrofuran, diethyl ether, diglyme, etc.), dimethylformamide, or a mixture of these solvents, at a temperature of about -60°C to about 50°C, preferably at a temperature from -30°C to room temperature, for about 10 minutes to about 15 25 hours. When lithium aluminum hydride or diboran is used as a reducing agent, anhydrous solvent such as diethyl ether, tetrahydrofuran, diglyme, etc., is preferably used.

When at least one of R<sup>15</sup> and R<sup>16</sup> in the compound (1y) is hydrogen atom, the compound is converted into the compound (1y) wherein at least one 30 of R<sup>15</sup> and R<sup>16</sup> is a lower alkyl group by reacting it with the compound (12) or

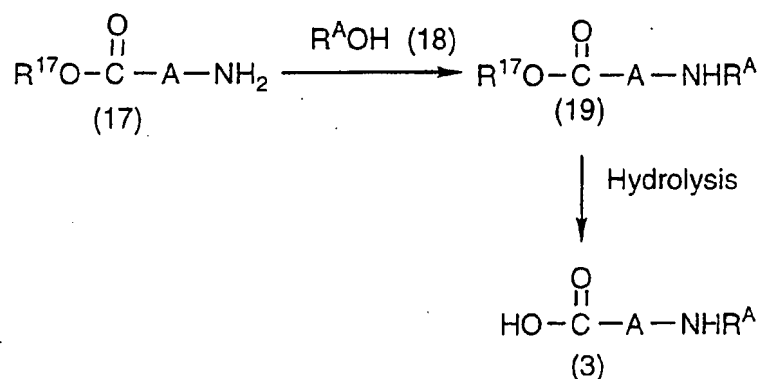


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the compound (13) under the same conditions as those of the reaction between the compound (1r) and the compound (12) or the compound (13) in Reaction Scheme-8.

The starting compound (3) or (4) can be prepared by the following processes.

Reaction Scheme-12

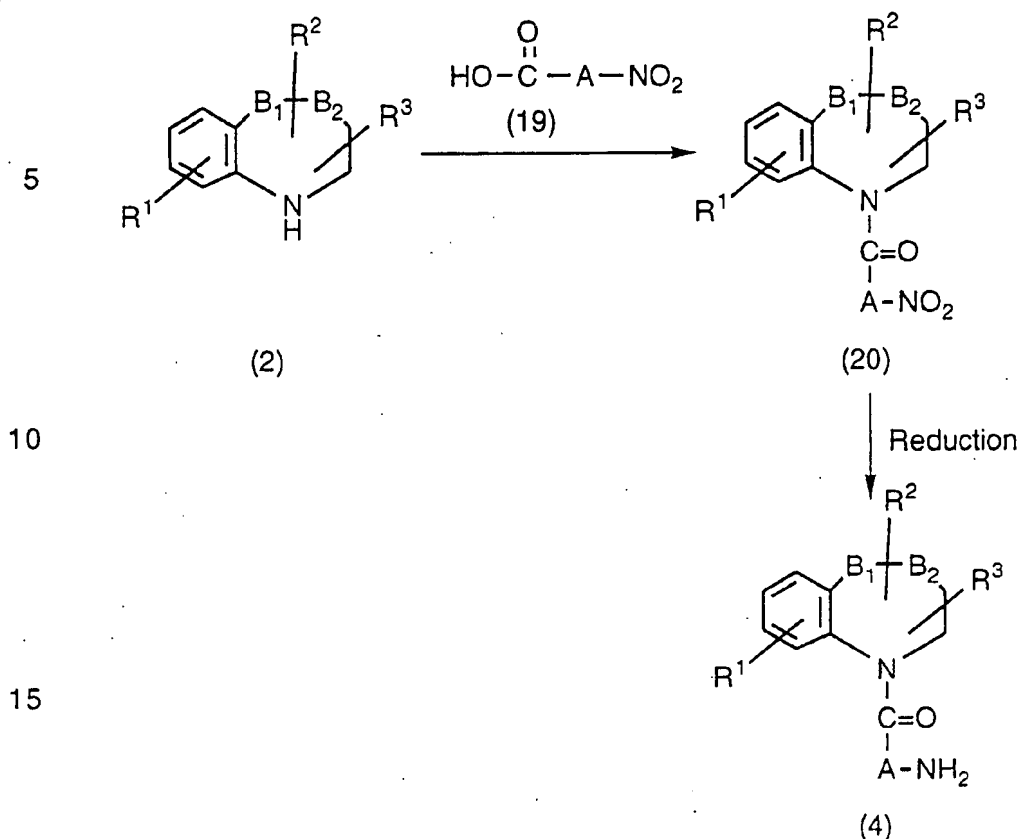


wherein  $\text{R}^{17}$  is a lower alkyl group, and  $\text{R}^{\text{A}}$  and A are the same as defined above.

The reaction between the compound (17) and the compound (18) is carried out under the same conditions as those of the reaction between the compound (2) and the compound (3) in Reaction Scheme-1.

The hydrolysis of the compound (19) is carried out under the same conditions as those of the hydrolysis of the compound (1g) in Reaction Scheme-5.

## Reaction Scheme-13



wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $A$ ,  $B_1$  and  $B_2$  are the same as defined above.

The reaction between the compound (2) and the compound (19) is carried out under the same conditions as those of the reaction between the compound (2) and the compound (3) in Reaction Scheme-1.

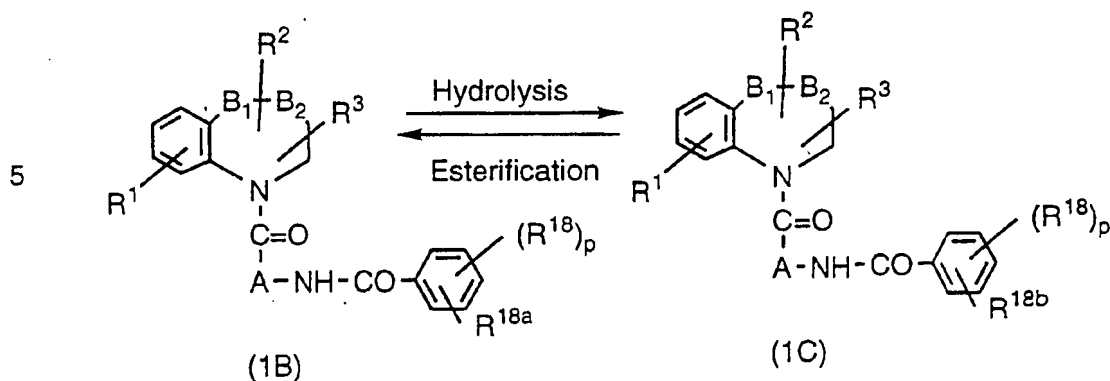
The reduction of the compound (20) is carried out, for example, (i) by using a reducing catalyst in an appropriate solvent, or (ii) by using a mixture of a metal or a metal salt and an acid, or a mixture of a metal or a metal salt and an alkali metal hydroxide, sulfide, ammonium salt, etc., as a reducing agent in an inert solvent.

When the method (i) is employed, the solvent includes, for example, water, acetic acid, alcohols (e.g. methanol, ethanol, isopropanol, etc.), hydrocarbons (e.g. hexane, cyclohexane, etc.), ethers (e.g. dioxane,

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tetrahydrofuran, diethyl ether, diethylene glycol dimethyl ether, etc.), esters (e.g. ethyl acetate, methyl acetate, etc.), aprotic polar solvents (e.g. N,N-dimethylformamide, etc.), or a mixture of these solvents. The reducing catalyst includes, for example, palladium, palladium-black, palladium-carbon, platinum, 5 platinum oxide, copper chromite, Ranney nickel, and the like. The catalyst is usually used in an amount of 0.02 to 1 mole to 1 mole of the starting compound. The reaction is usually carried out at a temperature from about -20°C to about 150°C, preferably at a temperature from 0°C to 100°C, under a pressure of 1 atm to 10 atms of hydrogen, for 0.5 to about 10 hours. An acid (e.g. 10 hydrochloric acid) may be added to the reaction system.

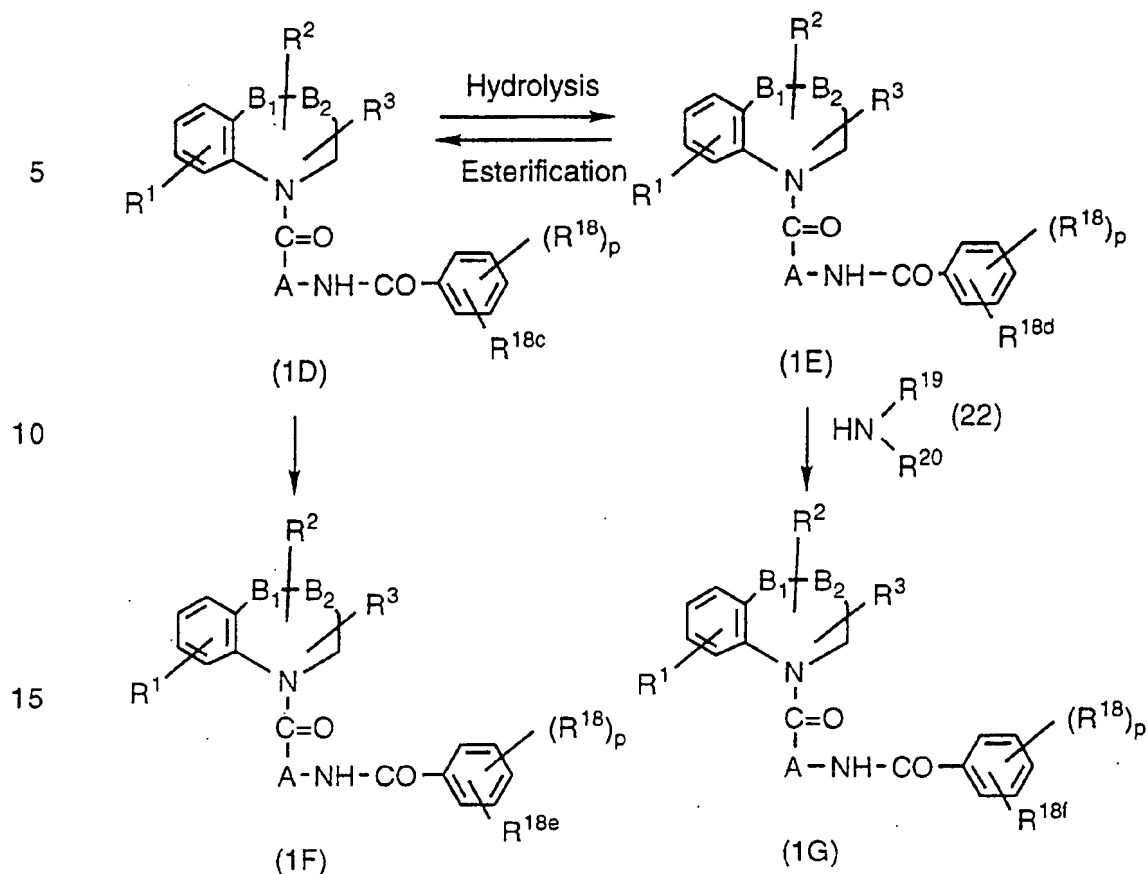
When the method (ii) is employed, there is used as a reducing agent a mixture of iron, zinc, tin or stannous chloride and a mineral acid (e.g. hydrochloric acid, sulfuric acid, etc.), or a mixture of iron, iron sulfide, zinc or tin and an alkali metal hydroxide (e.g. sodium hydroxide, etc.), sulfide (e.g. 15 ammonium sulfide, etc.), aqueous ammonia, ammonium salt (e.g. ammonium chloride, etc.). The inert solvent includes, for example, water, methanol, ethanol, dioxane, acetic acid, and the like. The conditions for reduction can be selected according to the kinds of the reducing agent to be used. For example, when a mixture of iron and hydrochloric acid is used as a reducing agent, the 20 reaction is preferably carried out at a temperature from 0°C to about 100°C, for 0.5 to about 10 hours. The reducing agent may be used at least in equimolar amount, usually in an amount of 1 mole to 20 moles to 1 mole of the starting compound.

Reaction Scheme-14

10 wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^{18}$ ,  $B_1$  and  $B_2$  are the same as defined above,  $p$  is 0, 1 or 2,  $R^{18a}$  is a lower alkoxycarbonyl group, and  $R^{18b}$  is carboxy group.

The hydrolysis of the compound (1B) is carried out under the same conditions as those of the hydrolysis of the compound (1g) in Reaction Scheme-5. The esterification of the compound (1C) is carried out under the same conditions as those of the esterification of the compound (1h) in Reaction Scheme-5.

15

Reaction Scheme-15

wherein  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^{18}$ ,  $\text{R}^{19}$ ,  $\text{R}^{20}$ ,  $p$ ,  $\text{B}_1$  and  $\text{B}_2$  are the same as defined above,

20  $\text{R}^{18c}$  is a lower alkoxy-carbonyl-substituted lower alkoxy group,  $\text{R}^{18d}$  is a carboxy-substituted lower alkoxy group,  $\text{R}^{18e}$  is a hydroxy-substituted lower alkoxy group, and  $\text{R}^{18f}$  is a group of the formula:  $-\text{O}-\text{E}-\text{CO}-\text{NR}^{19}\text{R}^{20}$  ( $\text{E}$ ,  $\text{R}^{19}$  and  $\text{R}^{20}$  are the same as defined above).

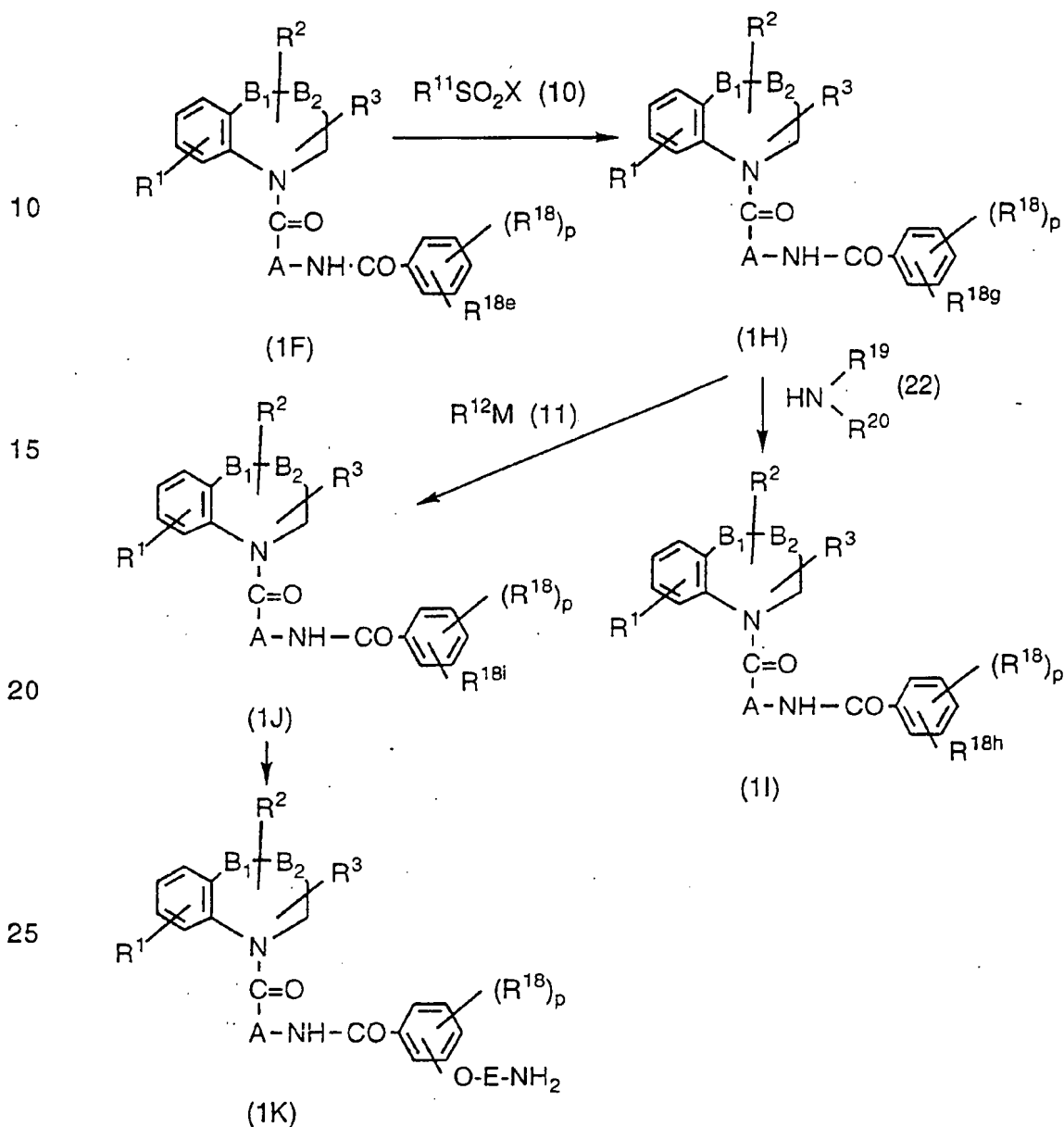
The hydrolysis of the compound (1D) is carried out under the same conditions as those of the hydrolysis of the compound (1g) in Reaction Scheme-5. The esterification of the compound (1E) is carried out under the same conditions as those of the esterification of the compound (1h) in Reaction Scheme-5.

The reaction of the compound (1E) with the compound (22) is carried out under the same conditions as those of the reaction between the compound

(2) and the compound (3) in Reaction Scheme-1.

The reaction of converting the compound (1D) into the compound (1F) is carried out under the same conditions as those of the reaction of converting the compound (1a) into the compound (1b) in Reaction Scheme-3.

5 Reaction Scheme-16



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wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>18</sup>, p, R<sup>18e</sup>, R<sup>11</sup>, X, E, R<sup>12</sup>, R<sup>19</sup>, R<sup>20</sup> and M are the same as defined above.

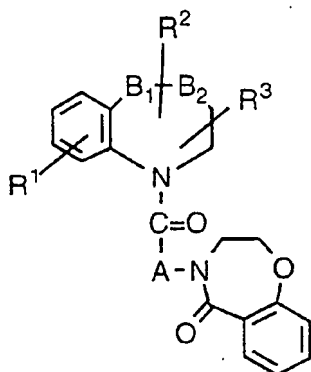
The reaction of the compound (1F) with the compound (10) is carried out under the same conditions as those of the reaction between the compound (1n) and the compound (10) in Reaction Scheme-7.

The reaction of the compound (1H) with the compound (22) is carried out under the same conditions as those of the reaction between the compound (1n) and the compound (10) in Reaction Scheme-7.

The reaction of the compound (1H) with the compound (11) is carried out under the same conditions as those of the reaction of the compound (1o) with the compound (11) in Reaction Scheme-7.

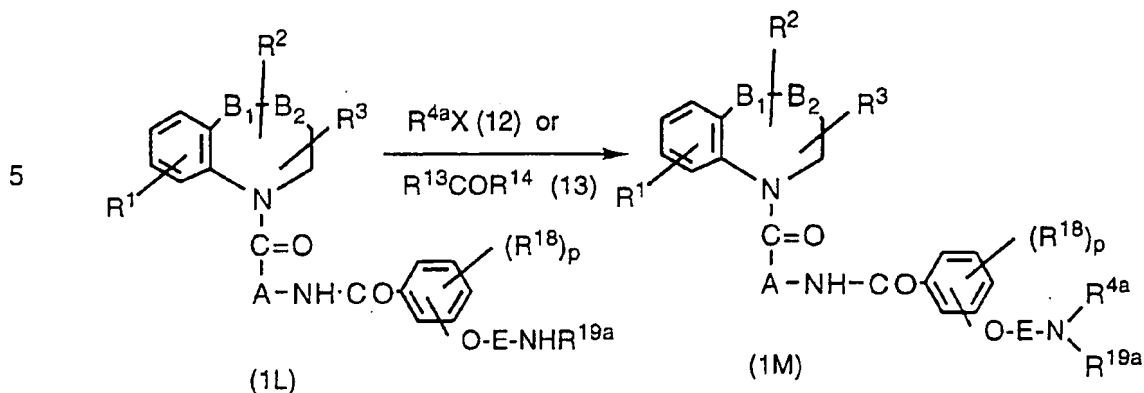
The reaction of converting the compound (1J) into the compound (1K) is carried out under the same conditions as those of the reaction of converting the compound (1p) into the compound (1q) in Reaction Scheme-7.

In this reaction, there may optionally be obtained a compound of the formula:



but which can easily be removed from the desired compounds.

## Reaction Scheme-17



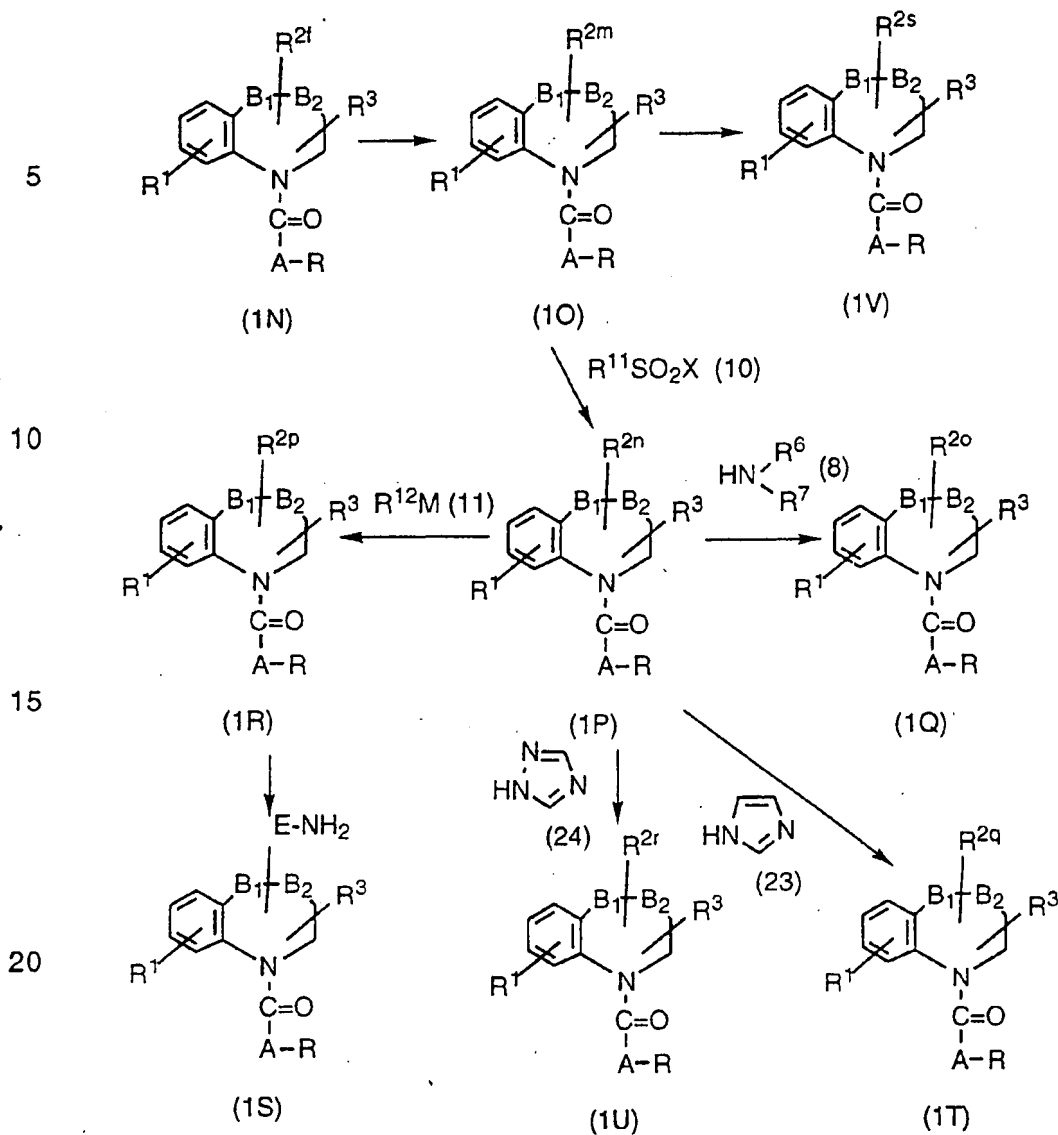
10 wherein  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^{18}$ ,  $\text{X}$ ,  $p$ ,  $\text{E}$ ,  $\text{R}^{4a}$ ,  $\text{R}^{13}$  and  $\text{R}^{14}$  are the same as defined above, and  $\text{R}^{19a}$  is hydrogen atom or a lower alkyl group.

The reaction of the compound (1L) with the compound (12) is carried out under the same conditions as those of the reaction between the compound (1r) and the compound (12) in Reaction Scheme-8. The reaction of the

15 compound (1L) with the compound (13) is carried out under the same conditions as those of the reaction between the compound (1r) and the compound (13) in Reaction Scheme-8.



## Reaction Scheme-18



wherein  $R$ ,  $R^1$ ,  $R^{2f}$ ,  $B_1$ ,  $B_2$ ,  $R^3$ ,  $R^{11}$ ,  $X$ ,  $R^{12}$ ,  $M$ ,  $R^6$  and  $R^7$  are the same as

defined above,  $R^{2m}$  is a hydroxy-substituted lower alkyl group,  $R^{2n}$  is a lower alkylsulfonyloxy-substituted lower alkyl group,  $R^{2o}$  is a group of the formula:

$-E-NR^6R^7$  ( $E$ ,  $R^6$  and  $R^7$  are the same as defined above),  $R^{2p}$  is a phthalimide-

substituted lower alkyl group,  $R^{2q}$  is an imidazolyl-substituted lower alkyl

group,  $R^{2r}$  is a 1,2,4-triazolyl-substituted lower alkyl group, and  $R^{2s}$  is a lower

alkanoyloxy-substituted lower alkyl group.

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The reaction of converting the compound (1N) into the compound (1O) is carried out under the same conditions as those of the reaction of converting the compound (1m) into the compound (1n) in Reaction Scheme-7. The reaction between the compound (1P) and the compound (8), the reaction of the compound (1P) with the compound (23) and the reaction of the compound (1P) with the compound (24) are carried out under the same conditions as those of the reaction of the compound (1n) with the compound (10) in Reaction Scheme-7.

The reaction of the compound (1P) with the compound (11) is carried out under the same conditions as those of the reaction of the compound (1o) with the compound (11) in Reaction Scheme-7.

The reaction of converting the compound (1R) into the compound (1S) is carried out under the same conditions as those of the reaction of converting the compound (1p) into the compound (1s) in Reaction Scheme-7.

The reaction of converting the compound (1O) into the compound (1V) is carried out by lower-alkanoylating the compound (1O) by using a compound of the formulae:  $(R^{22})_2O$  (26) or  $R^{22}X$  (27) [wherein  $R^{22}$  is a lower alkanoyl group, and X are the same as defined above]. This lower-alkanoylating reaction is carried out in the presence or absence of a basic compound. The basic compound includes, for example, alkali metals (e.g. sodium, potassium, etc.), hydroxides, carbonates, hydrogen carbonates of these alkali metals, or organic bases such as N,N-dimethylaminopyridine, pyridine, piperidine, and the like. The reaction can proceed either without a solvent, or in a solvent. The solvent includes, for example, ketones (e.g. acetone, methyl ethyle ketone, etc.), ethers (e.g. diethyl ether, dioxane, etc.), aromatic hydrocarbons (e.g. benzene, toluene, xylene, etc.), water, pyridine, and the like. The compounds (7) and (8) are used at least in equimolar amount to the starting compound, but they are preferably used in an amount of 1 mole to excess amount to 1 mole of the starting compound. The above reaction is carried out at a temperature from 0 to 200°C, preferably at about 0°C to about

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150°C, for 5 minutes to about 5 days.

Among the desired compounds (1) of the present invention, the compound (1) wherein the groups of R<sup>6</sup> and R<sup>7</sup> form a piperazine ring being substituted by a lower alkoxy carbonyl group at 4-position, can be hydrolyzed under the same conditions as those of the hydrolysis of the compound (1g) in Reaction Scheme-5, and converted into the compound (1) wherein the substituent at 4-position of said piperazine ring is hydrogen atom.

Among the compounds (1), the compound (1) wherein both R<sup>2</sup> and R<sup>3</sup> are a lower alkoxy group, and they bond at the same position, can be hydrolyzed under the same conditions as those of the hydrolysis of the compound (1g) in Reaction Scheme-5, and converted into the compound (1) wherein R<sup>2</sup> is oxo group.

Among the desired compounds (1) of the present invention, the compounds having an acidic group can easily be converted into salts by treating with a pharmaceutically acceptable basic compound. The basic compound includes, for example, metal hydroxides (e.g. sodium hydroxide, potassium hydroxide, lithium hydroxide, calcium hydroxide, etc.), alkali metal carbonates or hydrogen carbonates (e.g. sodium carbonate, sodium hydrogen carbonate, etc.) and alkali metal alcoholates (e.g. sodium methylate, potassium ethylate, etc.). Besides, among the desired compounds (1) of the present invention, the compounds having a basic group can easily be converted into acid addition salts thereof by treating with a pharmaceutically acceptable acid. The acid includes, for example, inorganic acids (e.g. sulfuric acid, nitric acid, hydrochloric acid, hydrobromic acid, etc.), and organic acids (e.g. acetic acid, p-toluenesulfonic acid, ethanesulfonic acid, oxalic acid, maleic acid, fumaric acid, citric acid, succinic acid, benzoic acid, etc.). These salts show as well excellent vasopressin antagonistic activity as the desired compounds (1).

In addition, the compounds (1) of the present invention include stereoisomers and optical isomers, and these isomers are also useful as vasopressin antagonist.

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The compounds of the present invention thus obtained can easily be isolated and purified by conventional isolation methods. The isolation methods are, for example, distillation method, recrystallization method, column chromatography, ion exchange chromatography, gel chromatography, affinity  
5 chromatography, preparative thin layer chromatography, extraction with a solvent, and the like.

The desired compounds (1) of the present invention and salts thereof are useful as a vasopressin antagonist, and are used in the form of a conventional pharmaceutical preparation. The preparation is prepared by  
10 using conventional diluents or carriers such as fillers, thickening agents, binders, wetting agent, disintegrators, surfactants, lubricants, and the like. The pharmaceutical preparations can be selected from various forms in accordance with the desired utilities, and the representative forms are tablets, pills, powders, solutions, suspensions, emulsions, granules, capsules,  
15 suppositories, injections (solutions, suspensions, etc.), and the like. In order to form in tablets, there are used carriers such as vehicles (e.g. lactose, white sugar, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, crystalline cellulose, silicic acid, etc.), binders (e.g. water, ethanol, propanol, simple syrup, glucose solution, starch solution, gelatin solution, carboxymethyl  
20 cellulose, shellac, methyl cellulose, potassium phosphate, polyvinylpyrrolidone, etc.), disintegrators (e.g. dry starch, sodium alginate, agar powder, laminaran powder, sodium hydrogen carbonate, calcium carbonate, polyoxyethylene sorbitan fatty acid esters, sodium laurylsulfate, stearic monoglyceride, starches, lactose, etc.), disintegration inhibitors (e.g. white  
25 sugar, stearin, cacao butter, hydrogenated oils, etc.), absorption promoters (e.g. quaternary ammonium base, sodium laurylsulfate, etc.), wetting agents (e.g. glycerin, starches, etc.), adsorbents (e.g. starches, lactose, kaolin, bentonite, colloidal silicates, etc.), lubricants (e.g. purified talc, stearates, boric acid powder, polyethylene glycol, etc.), and the like. Moreover, the tablets may also  
30 be in the form of a conventional coated tablet, such as sugar-coated tablets, gelatin-coated tablets, enteric coated tablets, film coating tablets, or double or

multiple layer tablets. In the preparation of pills, the carriers include vehicles (e.g. glucose, lactose, starches, cacao butter, hydrogenated vegetable oils, kaolin, talc, etc.), binders (e.g. gum arabic powder, tragacanth powder, gelatin, ethanol, etc.), disintegrators (e.g. laminaran, agar, etc.), and the like. In the preparation of suppositories, the carriers include, for example, polyethylene glycol, cacao butter, higher alcohols, higher alcohol esters, gelatin, semi-synthetic glycerides, and the like. Capsules can be prepared by charging a mixture of the compound of the present invention and the above carriers into hard gelatin capsules or soft capsules in usual manner. In the preparation of injections, the solutions, emulsions and suspensions are sterilized and are preferably made isotonic with the blood. In the preparation of these solutions, emulsions and suspensions, there are used conventional diluents, such as water, ethyl alcohol, macrogol, propylene glycol, ethoxylated isostearyl alcohol, polyoxylated isostearyl alcohol, polyoxyethylene sorbitan fatty acid esters, and the like. In this case, the pharmaceutical preparations may also be incorporated with sodium chloride, glucose, or glycerin in an amount sufficient to make them isotonic, and may also be incorporated with conventional solubilizers, buffers, anesthetizing agents. Besides, the pharmaceutical preparations may optionally be incorporated with coloring agent, preservatives, perfumes, flavors, sweetening agents, and other medicaments, if required.

The amount of the desired compound of the present invention to be incorporated into the vasopressin antagonist is not specified but may be selected from a broad range, but usually, it is preferably in the range of 1 to 70 % by weight, more preferably 5 to 50 % by weight.

The vasopressin antagonist containing as an active ingredient the compounds (1) of the present invention and a salt thereof may be administered in any method, and suitable method for administration may be determined in accordance with various forms of preparations, ages, sexes and other conditions of the patients, the degree of severity of diseases, and the like. For example, tablets, pills, solutions, suspensions, emulsions, granules and capsules are administered orally. The injections are intravenously

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administered alone or together with a conventional auxiliary liquid (e.g. glucose, amino acid solutions), and further are optionally administered alone in intramuscular, intracutaneous, subcutaneous, or intraperitoneal route, if required. Suppositories are administered in intrarectal route.

- 5           The dosage of the vasopressin antagonist of the present invention may be selected in accordance with the usage, ages, sexes and other conditions of the patients, the degree of severity of the diseases, and the like, but it is usually in the range of about 0.6 to 50 mg of the active compound of the present invention per 1 kg of body weight of the patient per day. The active  
10       compound is preferably contained in an amount of about 10 to about 1000 mg per the dosage unit.

#### Best Mode for Carrying Out the Invention

##### Examples

- 15           The present invention is illustrated in more detail by the following Preparations of vasopressin antagonist, Reference Examples of processes for preparing the starting compounds to be used for preparing the desired compounds of the present invention, and Examples of processes for preparing the desired compounds, and Experiments of the activities of the desired compounds of the present invention.

##### 20           Preparation 1

Film coated tablets are prepared from the following compounds.

	<u>Components</u>	<u>Amount</u>
25	5-Hydroxy-7-chloro-1-[6-(2-methylbenzoyl-amino)nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine	150 g
	Avicel (trade name of microcrystalline cellulose manufactured by Asahi Chemical Industry, Co., Ltd. Japan)	40 g
	Corn starch	30 g
30	Magnesium stearate	2 g
	Hydroxypropyl methylcellulose	10 g
	Polyethylene glycol-6000	3 g

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Castor oil	40 g
Ethanol	40 g

The active compound of the present invention, Avicel, corn starch and magnesium stearate are mixed and kneaded and the mixture is tabletted using a conventional pounder (R 10 mm) for sugar coating. The tablets thus obtained are coated with a film coating agent consisting of hydroxypropyl methylcellulose, polyethylene glycol-6000, castor oil and ethanol to give film coated tablets.

#### Preparation 2

Tablets are prepared from the following components.

	<u>Components</u>	<u>Amount</u>
	5-Hydroxy-7-chloro-1-[2-(5-methylbenzoylamino)-thenoyl]-2,3,4,5-tetrahydro-1H-benzazepine	150 g
	Citric acid	1.0 g
15	Lactose	33.5 g
	Dicalcium phosphate	70.0 g
	Pullonic F-68	30.0 g
	Sodium laurylsulfate	15.0 g
	Polyvinylpyrrolidone	15.0 g
20	Polyethylene glycol (Carbowax 1500)	4.5 g
	Polyethylene glycol (Carbowax 6000)	45.0 g
	Corn starch	30.0 g
	Dry sodium stearate	3.0 g
	Dry magnesium stearate	3.0 g
25	Ethanol	q.s.

The active compound of the present invention, citric acid, lactose, dicalcium phosphate, Pullonic F-68 and sodium laurylsulfate are mixed. The mixture is screened with No. 60 screen and is granulated with an alcohol solution containing polyvinylpyrrolidone, Carbowax 1500 and 6000. If required, an alcohol is added thereto so that the powder mixture is made a paste-like mass. Corn starch is added to the mixture and the mixture is

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continuously mixed to form uniform particles. The resulting particles are passed through No. 10 screen and entered into a tray and then dried in an oven at 100°C for 12 to 14 hours. The dried particles are screened with No. 16 screen and thereto are added dry sodium laurylsulfate and dry magnesium stearate, and the mixture is tabletted to form the desired shape.

The core tablets thus prepared are vanished and dusted with talc in order to guard from wetting. Undercoating is applied to the core tablets. In order to administer the tablets orally, the core tablets are vanished several times. In order to give round shape and smooth surface to the tablets, further undercoating and coating with lubricant are applied thereto. The tablets are further coated with a coloring coating material until the desired colored tablets are obtained. After drying, the coated tablets are polished to obtain the desired tablets having uniform gloss.

#### Preparation 3

An injection preparation is prepared from the following components.

<u>Components</u>	<u>Amount</u>
5-Hydroxy-7-chloro-1-[2-(2-methylbenzoyl-amino)-5-thiazolylcarbonyl]-2,3,4,5-tetrahydro-1H-benzazepine	5 g
Polyethylene glycol (molecular weight: 4000)	0.3 g
Sodium chloride	0.9 g
Polyoxyethylene sorbitan monooleate	0.4 g
Sodium metabisulfite	0.1 g
Methyl-paraben	0.18 g
Propyl-paraben	0.02 g
Distilled water for injection	10.0 ml

The above parabens, sodium metabisulfite and sodium chloride are dissolved with stirring in distilled water of half volume of the above with stirring at 80°C. The solution thus obtained is cooled to 40°C, and the active compound of the present invention and further polyethylene glycol and polyoxyethylene sorbitan monooleate are dissolved in the above solution. To



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the solution is added distilled water for injection to adjust to the desired volume, and the solution is sterilized by filtering with an appropriate filter paper to give an injection preparation.

Reference Example 1

5                   To 6-nitronicotinic acid (3.5 g) is added thionyl chloride (50 ml), and the mixture is refluxed for three hours, and evaporated to remove thionyl chloride to give 6-nitronicotinoyl chloride, which is added with stirring to a solution of 7-chloro-5-oxo-2,3,4,5-tetrahydro-1H-benzazepine (3.4 g) in pyridine (50 ml) under ice-cooling. The mixture is stirred at room temperature  
10 overnight. To the reaction mixture is added water, and the mixture is extracted with ethyl acetate. The extract is washed successively with 0.1 N aqueous hydrochloric acid and water, and dried over magnesium sulfate. The resultant is evaporated under reduced pressure to remove the solvent, and the residue is purified by silica gel column chromatography to give 7-chloro-5-oxo-1-(6-nitronicotinoyl)-2,3,4,5-tetrahydro-1H-benzazepine (4.9 g) as colorless  
15 amorphous.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  : 1.85 - 2.60 (2H, m), 2.75 - 2.95 (2H, m), 3.10 - 4.00 (1H, m), 4.20 - 5.20 (1H, m), 6.55 - 6.75 (1H, m), 7.15 - 7.30 (1H, m), 7.75 - 7.90 (2H, m), 8.12 (1H, d,  $J=8.3$  Hz), 8.46 (1H, s)

20                   Reference Example 2

2N Hydrochloric acid (50 ml) is added to reduced iron (23.5 g), and the mixture is allowed to stand for 10 minutes. The mixture is filtered, and washed with water and acetone, and then, dried. To 7-chloro-5-oxo-1-(6-nitronicotinoyl)-2,3,4,5-1H-tetrahydro-benzazepine (9.4 g) is added acetic acid  
25 (100 ml), and thereto is added gradually the above reduced iron at 80°C. The mixture is stirred at the same temperature for 30 minutes, and filtered on Celite. The filtrate is neutralized with sodium hydrogen carbonate, and extracted with dichloromethane. The extract is washed with water, and dried over magnesium sulfate. The resultant is evaporated under reduced pressure to remove the  
30 solvent, and the residue is purified by silica gel column chromatography, and

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further recrystallized from dichloromethane-diethyl ether to give 7-chloro-5-oxo-1-(6-aminonicotinoyl)-2,3,4,5-tetrahydro-1H-benzazepine (6.5 g) as white powder.

M.p. 210 - 213 °C

5

Reference Example 3

Using the suitable starting compounds, the following compounds are obtained in the same manner as in Reference Example 1.

7-Chloro-5-methoxycarbonylmethyl-1-(6-nitronicotinoyl)-2,3,4,5-tetrahydro-1H-benzazepine

10

White powder

M.p. 162 - 165°C (recrystallized from dichloromethane-diethyl ether)

7-Chloro-5-methoxycarbonylmethoxy-1-(6-nitronicotinoyl)-2,3,4,5-tetrahydro-1H-benzazepine

White powder

15

M.p. 154 - 157°C (recrystallized from dichloromethane-diethyl ether)

7-Chloro-1-(6-nitronicotinoyl)-2,3,4,5-tetrahydro-1H-benzazepine

White powder

M.p. 171 - 174°C (recrystallized from dichloromethane-diethyl ether)

20

7-Chloro-4-methyl-1-(6-nitronicotinoyl)-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine

Colorless amorphous

25

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 2.44 (3H, s), 3.00 - 3.30 (3H, m), 3.73 (1H, d, J=14.1 Hz), 4.02 (1H, d, J=14.1 Hz), 4.80 - 4.95 (1H, m), 6.56 (1H, d, J=8.3 Hz), 7.00 (1H, dd, J=2.4, 8.3 Hz), 7.15 - 7.60 (1H, m), 7.92 (1H, dd, J=2.1, 8.3 Hz), 8.14 (1H, d, J=8.2 Hz), 8.36 (1H, d, J=1.7 Hz)

7-Chloro-5-oxo-1-(5-nitrothenoyl)-2,3,4,5-tetrahydro-1H-benzazepine

White powder

M.p. 166 - 169°C (recrystallized from dichloromethane-diethyl ether)

7-Chloro-5-oxo-1-(5-nitro-2-furoyl)-2,3,4,5-tetrahydro-1H-benzazepine

30

White powder

- 49 -

M.p. 124 - 126°C (recrystallized from dichloromethane-diethyl ether)

7-Chloro-5-oxo-1-(5-nitro-2-thiazolyl)-2,3,4,5-tetrahydro-1H-benzazepine

White powder

M.p. 149 - 152°C (recrystallized from dichloromethane-diethyl ether)

5        7-Chloro-5-oxo-1-(5-nitro-1-pyridylcarbonyl)-2,3,4,5-tetrahydro-1H-benzazepine

Yellow powder

1H-NMR (CDCl<sub>3</sub>) δ : 1.70 - 2.75 (2H, m), 2.80 - 3.70 (3H, m), 4.60 - 5.30 (1H, m), 6.59 (1H, d, J=8.3 Hz), 7.15 (1H, dd, J=2.4, 8.3 Hz), 7.89 (1H, d, J=2.4 Hz), 7.94 (1H, d, J=8.6 Hz), 8.52 (1H, dd, J=2.4, 8.5 Hz), 9.02 (1H, d, J=2.4 Hz)

7-Chloro-5-methyl-1-(6-nitronicotinoyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine

Orange powder

15        M.p. 162.5 - 164°C (recrystallized from dichloromethane-diethyl ether)

Reference Example 4

Using the suitable starting compounds, the following compounds are obtained in the same manner as in Reference Example 2.

20        7-Chloro-5-methoxycarbonylmethyl-1-(6-aminonicotinoyl)-2,3,4,5-tetrahydro-1H-benzazepine

White powder

M.p. 201 - 204°C (recrystallized from dichloromethane-diethyl ether)

25        7-Chloro-5-methoxycarbonylmethoxy-1-(6-aminonicotinoyl)-2,3,4,5-tetrahydro-1H-benzazepine

Colorless amorphous

1H-NMR (CDCl<sub>3</sub>) δ : 1.60 - 2.60 (4H, m), 2.60 - 3.00 (1H, m), 3.77 (3H, s), 4.05 - 4.45 (2H, m), 4.50 - 5.20 (2H, m), 4.70 (2H, s), 6.30 (1H, d, J=8.6 Hz), 6.60 - 6.75 (1H, m), 7.05 (1H, d, J=2.4, 8.3 Hz), 7.10 - 7.70 (2H, m), 7.80 - 8.15 (1H, m)

## 7-Chloro-1-(6-aminonicotinoyl)-2,3,4,5-tetrahydro-1H-benzazepine

White powder

M.p. 228 - 231°C (recrystallized from dichloromethane-diethyl ether)

## 7-Chloro-4-methyl-1-(6-aminonicotinoyl)-2,3,4,5-tetrahydro-1H-1,4-

5 benzodiazepine

Colorless amorphous

 $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  : 2.41 (3H, s), 3.00 (3H, s), 3.67 (1H, d,  $J=14$  Hz),3.99 (1H, d,  $J=14$  Hz), 4.68 (2H, s), 4.80 - 5.10 (1H, m), 6.28 (1H, d,  $J=8.6$  Hz),6.66 (1H, d,  $J=8.4$  Hz), 7.02 (1H, dd,  $J=2.4, 8.4$  Hz), 7.29 (1H, d,  $J=2.3$  Hz), 7.3210 (1H, dd,  $J=2.3, 8.6$  Hz), 7.90 (1H, d,  $J=2.3$  Hz)

## 7-Chloro-5-oxo-1-(5-aminothenoyl)-2,3,4,5-tetrahydro-1H-benzazepine

Yellow powder

 $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  : 2.00 - 2.25 (2H, m), 2.65 - 2.85 (2H, m), 3.75 -4.70 (4H, m), 5.83 (1H, d,  $J=4.1$  Hz), 6.40 (1H, d,  $J=4.1$  Hz), 7.16 (1H, d,  $J=8.4$ 15 Hz), 7.42 (1H, dd,  $J=2.5, 8.4$  Hz), 7.87 (1H, d,  $J=2.5$  Hz)

## 7-Chloro-5-oxo-1-(5-amino-2-furoyl)-2,3,4,5-tetrahydro-1H-benzazepine

Green powder

M.p. 151 - 154°C (recrystallized from dichloromethane-diethyl ether)

## 7-Chloro-5-oxo-1-(5-amino-2-thiazolyl)-2,3,4,5-tetrahydro-1H-

20 benzazepine

Yellow powder

M.p. 142 - 144.5°C (recrystallized from dichloromethane-diethyl

ether)

## 7-Chloro-5-oxo-1-(5-amino-2-pyridylcarbonyl)-2,3,4,5-tetrahydro-1H-1,5-

25 benzazepine

Yellow powder

M.p. 143 - 144.5°C (recrystallized from dichloromethane-diethyl

ether)

## 7-Chloro-5-methyl-1-(6-aminonicotinoyl)-2,3,4,5-tetrahydro-1H-1,5-

30 benzodiazepine

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White powder

M.p. 191 - 193°C (recrystallized from dichloromethane-diethyl ether)

Reference Example 5

5 To a solution of 6-aminonicotinic acid methyl ester (4 g) in pyridine (40 ml) is added with stirring 2-methylbenzoyl chloride (6.73 g) under ice-cooling, and the mixture is stirred at room temperature overnight. To the reaction solution is added water, and the precipitated crystals are collected by filtration, and dried to give 6-(2-methylbenzoylamino)nicotinic acid methyl ester (5.7 g) as white powder.

10 M.p. 167 - 169°C

Reference Example 6

To a solution of 6-(2-methylbenzoylamino)nicotinic acid methyl ester (2.1 g) in methanol (30 ml) is added 5 % aqueous sodium hydroxide solution (24 ml), and the mixture is refluxed for two hours. To the reaction solution is added water, and the mixture is made weak acidic with 1N aqueous hydrochloric acid solution, and then, extracted with diethyl ether. The extract is dried over magnesium sulfate, and evaporated under reduced pressure to remove the solvent to give 6-(2-methylbenzoylamino)nicotinic acid (2.1 g) as white powder.

20 M.p. 235 - 238°C

Reference Example 7

Using the suitable starting compounds, there are obtained the following compounds in the same manner as in Reference Example 1.

25 7-Chloro-5-methoxy-1-(6-nitronicotinoyl)-2,3,4,5-tetrahydro-1H-benzazepine

Yellow powder

M.p. 173 - 175°C (recrystallized from dichloromethane-diethyl ether)

7-Chloro-5-allyloxy-1-(6-nitronicotinoyl)-2,3,4,5-tetrahydro-1H-benzazepine

30 Yellow powder

M.p. 116 - 120°C (recrystallized from dichloromethane-diethyl ether)

Reference Example 8

Using the suitable starting compounds, there are obtained the following compounds in the same manner as in Reference Example 2.

7-Chloro-5-methoxy-1-(6-aminonicotinoyl)-2,3,4,5-tetrahydro-1H-  
5 benzazepine  
Colorless amorphous  
 $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  : 1.40 - 2.55 (4H, m), 2.55 - 3.00 (1H, m), 3.30 -  
3.60 (3H, m), 4.20 - 5.20 (2H, m), 4.66 (2H, brs), 6.30 (1H, d,  $J=8.5$  Hz), 6.66  
(1H, d,  $J=8.4$  Hz), 7.03 (1H, dd,  $J=2.4, 8.3$  Hz), 7.30 - 7.65 (2H, m), 7.80 - 8.10  
10 (1H, m)

7-Chloro-5-allyloxy-1-(6-aminonicotinoyl)-2,3,4,5-tetrahydro-1H-  
benzazepine  
Colorless amorphous  
 $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  : 1.50 - 2.60 (4H, m), 2.60 - 3.00 (1H, m), 4.00 -  
15 4.30 (2H, m), 4.40 - 4.80 (4H, m), 5.00 - 5.50 (2H, m), 5.80 - 6.20 (1H, m), 6.29  
(1H, d,  $J=8.4$  Hz), 6.65 (1H, d,  $J=8.3$  Hz), 7.03 (1H, dd,  $J=2.3, 8.3$  Hz), 7.10 -  
7.70 (2H, m), 7.80 - 8.10 (1H, m)

Example 1

To a solution of 7-chloro-5-oxo-1-(6-aminonicotinoyl)-2,3,4,5-  
20 tetrahydro-1H-benzazepine (0.25 g) in pyridine (2 ml) is added with stirring 2-  
methylbenzoyl chloride (0.18 g) under ice-cooling, and the mixture is stirred at  
room temperature for one hour. To the reaction solution is added water, and  
the mixture is extracted with ethyl acetate. The extract is washed successively  
with 0.1 N aqueous hydrochloric acid solution and water, and dried over  
25 magnesium sulfate. The resultant is evaporated under reduced pressure to  
remove the solvent, and the residue is purified by silica gel column  
chromatography to give 7-chloro-5-oxo-1-[6-(2-methylbenzoylamino)-  
nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (0.3 g) as colorless amorphous.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  : 2.0 - 2.4 (2H, m), 2.50 (3H, s), 2.89 (2H, t,  $J=6.2$   
30 Hz), 3.2 - 5.0 (2H, br), 6.72 (1H, d,  $J=8.4$  Hz), 7.20 - 7.51 (5H, m), 7.60 (1H, dd,

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J=2.3, 8.7 Hz), 7.86 (1H, d, J=2.5 Hz), 8.09 (1H, d, J=1.7 Hz), 8.24 (1H, d, J=8.7 Hz), 8.50 (1H, s)

### Example 2

To a solution of 7-chloro-5-oxo-1-[6-(2-methylbenzoylamino)-  
5 nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (0.3 g) in methanol (5 ml) is added with stirring sodium borohydride (0.05 g) under ice-cooling, and the mixture is stirred at room temperature for one hour. To the reaction solution is added water, and the mixture is extracted with dichloromethane. The extract is washed with water, and dried over magnesium sulfate. The resultant is  
10 evaporated under reduced pressure to remove the solvent, and the residue is purified by silica gel column chromatography to give 7-chloro-5-hydroxy-1-[6-(2-methylbenzoylamino)nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (0.2 g) as colorless amorphous.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.60 - 2.60 (4H, m), 2.46 (3H, s), 2.70 - 2.95 (1H,  
15 m), 3.73 (1H, s), 4.65 - 5.65 (2H, m), 6.57 (1H, d, J=8.1 Hz), 7.00 (1H, d, J=6.5 Hz), 7.15 - 8.40 (8H, m), 8.70 - 8.90 (1H, m)

### Example 3

To a suspension of methyltriphenylphosphonium bromide (0.86 g) in tetrahydrofuran (20 ml) is added with stirring potassium t-butoxide (0.23 g) at  
20 -5°C, and the mixture is stirred at -5°C for one hour. To the mixture is added 7-chloro-5-oxo-1-[6-(2-methylbenzoylamino)nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (0.58 g) at the same temperature, and the mixture is stirred at room temperature for one hour. The reaction mixture is poured into ice-water, and extracted with ethyl acetate. The extract is washed with water, dried over  
25 magnesium sulfate, and evaporated under reduced pressure to remove the solvent. The residue is purified by silica gel column chromatography to give 7-chloro-5-methylenedioxy-1-[6-(2-methylbenzoylamino)nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (0.28 g) as yellow amorphous.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.85 - 2.20 (2H, m), 2.30 - 3.30 (3H, m), 2.50  
30 (3H, s), 4.75 - 5.15 (1H, m), 5.20 - 5.35 (2H, m), 6.61 (1H, d, J=8.3 Hz), 7.01

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(1H, dd, J=2.5, 8.4 Hz), 7.20 - 7.60 (6H, m), 8.06 (1H, d, J=2 Hz), 8.19 (1H, d, J=8.7 Hz), 8.34 (1H, s)

#### Example 4

To a solution of 7-chloro-5-methylidene-1-[6-(2-methylbenzoyl-  
5 amino)nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (0.28 g) in t-butanol (3 ml), pyridine (0.2 ml) and water (1.2 ml) is added 4 % aqueous osmium tetraoxide solution (0.2 ml), and further thereto is added 4-methylmorpholine N-oxide (0.1 g). The mixture is refluxed for 5 hours, and cooled. Saturated aqueous sodium hydrogen sulfite solution is added to the reaction mixture, and  
10 the mixture is stirred at room temperature for 30 minutes. Water is added to the reaction solution, and the mixture is extracted with a mixture of ethyl acetate and tetrahydrofuran. The extract is washed with water, dried over magnesium sulfate, and evaporated under reduced pressure to remove the solvent. The residue is purified by silica gel column chromatography to give 7-chloro-5-  
15 hydroxymethyl-5-hydroxy-1-[6-(2-methylbenzoylamino)nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (0.14 g) as colorless amorphous.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.50 - 2.60 (3H, m), 2.45 (3H, s), 2.60 - 2.95 (1H, m), 3.60 - 4.25 (4H, m), 4.70 - 5.10 (1H, m), 6.54 (1H, d, J=8.3 Hz), 6.99 (1H, dd, J=2.3, 8.3 Hz), 7.10 - 7.70 (5H, m), 7.82 (1H, d, J=2.3 Hz), 8.10 - 8.30 (2H, m),  
20 8.83 (1H, s)

#### Example 5

To a suspension of 7-chloro-5-methoxycarbonylmethyl-1-[6-(2-methylbenzoylamino)nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (1.6 g) in ethanol (20 ml) is added 5 N aqueous sodium hydroxide solution (4 ml), and  
25 the mixture is stirred at room temperature for 4 hours. Water is added to the reaction solution, and the mixture is made weak acidic with diluted hydrochloric acid, and extracted with dichloromethane. The extract is washed with water, dried over magnesium sulfate, and evaporated under reduced pressure to remove the solvent. The residue is crystallized from diethyl ether, and further  
30 recrystallized from diethyl ether to give 7-chloro-5-carboxymethyl-1-[6-(2-



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methylbenzoylamino)nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (1.5 g) as white powder.

M.p. 187 - 190°C

Example 6

5 To a solution of 7-chloro-5-carboxymethyl-1-[6-(2-methylbenzoyl-amino)nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (0.35 g) in dichloro-methane (10 ml) is added with stirring N,N-bis(2-oxo-3-oxazolydiny)-phosphinic chloride (0.24 g) under ice-cooling, and the mixture is stirred at room temperature for 15 minutes. To the mixture are added with stirring  
10 dimethylamine hydrochloride (0.078 g) and triethylamine (0.31 ml) under ice-cooling, and the mixture is stirred at room temperature overnight. Water is added to the reaction solution, and the mixture is extracted with dichloro-methane. The extract is washed successively with diluted aqueous sodium hydroxide solution and water, dried over magnesium sulfate, and evaporated  
15 under reduced pressure to remove the solvent. The residue is purified by silica gel column chromatography, and recrystallized from dichloromethane-diethyl ether to give 7-chloro-5-dimethylaminocarbonylmethyl-1-[6-(2-methylbenzoyl-amino)nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (0.29 g) as white powder.

M.p. 197 - 198.5°C

20

Example 7

To a suspension of 7-chloro-5-methoxycarbonylmethoxy-1-[6-(2-methylbenzoylamino)nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (0.4 g) in ethanol (5 ml) is added 5 N aqueous sodium hydroxide solution (1 ml), and the mixture is stirred at room temperature for 4 hours. Water is added to the  
25 reaction mixture, and the mixture is made weak acidic by adding thereto diluted hydrochloric acid, and extracted with dichloromethane. The extract is washed with water, dried over magnesium sulfate, and evaporated under reduced pressure to remove the solvent. The residue is crystallized from diethyl ether to give 7-chloro-5-carboxymethoxy-1-[6-(2-methylbenzoylamino)nicotinoyl]-  
30 2,3,4,5-tetrahydro-1H-benzazepine (0.38 g) as white powder.

M.p. 220 - 222°C

Example 8

To a solution of 7-chloro-5-carboxymethoxy-1-[6-(2-methylbenzoylamino)nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (0.3 g) in dichloromethane (10 ml) is added with stirring N,N-bis(2-oxo-3-oxazolidinyl)phosphinic chloride (0.2 g) under ice-cooling, and the mixture is stirred at room temperature for 15 minutes. Subsequently, to the mixture are added with stirring N-methylpiperazine (0.09 ml) and triethylamine (0.17 ml) under ice-cooling, and the mixture is stirred at room temperature overnight. Water is added to the reaction solution, and the mixture is extracted with dichloromethane. The extract is washed with water, dried over magnesium sulfate, and evaporated under reduced pressure to remove the solvent. The residue is purified by silica gel column chromatography to give 7-chloro-5-[(4-methyl-1-piperazinyl)carbonylmethoxy]-1-[6-(2-methylbenzoylamino)nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (0.23 g) as colorless amorphous.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.60 - 2.60 (8H, m), 2.29, 2.32 (3H, s), 2.50 (3H, s), 2.70 - 3.05 (1H, m), 3.40 - 3.80 (4H, m), 4.10 - 4.50 (2H, m), 4.55 - 5.20 (2H, m), 6.60 - 6.75 (1H, m), 7.00 - 7.15 (1H, m), 7.15 - 7.85 (6H, m), 8.10 - 8.40 (3H, m)

Example 9

To a solution of 7-chloro-5-methoxycarbonylmethoxy-1-[6-(2-methylbenzoylamino)nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (1.2 g) in tetrahydrofuran (15 ml) is added with stirring lithium borohydride (0.1 g) under ice-cooling, and the mixture is stirred at room temperature overnight. Water is added to the reaction solution, and the mixture is extracted with ethyl acetate. The extract is washed with water, dried over magnesium sulfate, and evaporated under reduced pressure to remove the solvent. The residue is purified by silica gel column chromatography to give 7-chloro-5-(2-hydroxyethoxy)-1-[6-(2-methylbenzoylamino)nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (0.73 g) as colorless amorphous.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.50 - 2.60 (4H, m), 2.51 (3H, s), 2.70 - 3.05 (1H,

m), 3.50 - 4.05 (4H, m), 4.50 - 5.15 (2H, m), 6.60 - 6.75 (1H, m), 7.00 - 7.15 (1H, m), 7.20 - 7.85 (6H, m), 8.10 - 8.40 (3H, m)

#### Example 10

To a solution of 7-chloro-5-(2-hydroxyethoxy)-1-[6-(2-methylbenzoyl-  
5 amino)nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (0.6 g) in pyridine (5 ml) is added with stirring methanesulfonyl chloride (0.11 ml) under ice-cooling, and the mixture is stirred at room temperature for two hours. Water is added to the reaction solution, and the mixture is extracted with dichloromethane. The  
10 extract is washed with water, dried over magnesium sulfate, and evaporated under reduced pressure to remove the solvent. The residue is purified by silica gel column chromatography to give 7-chloro-5-(2-methanesulfonyloxyethoxy)-1-[6-(2-methylbenzoylamino)nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (0.55 g) as colorless amorphous.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.50 - 2.60 (4H, m), 2.50 (3H, s), 2.70 - 3.20 (1H,  
15 m), 2.93, 3.13 (3H, s), 3.70 - 4.05 (2H, m), 4.20 - 5.20 (4H, m), 6.64 (1H, d, J=8.1 Hz), 7.00 - 7.10 (1H, m), 7.20 - 7.85 (6H, m), 8.05 - 8.40 (3H, m)

#### Example 11

To a solution of 7-chloro-5-(2-methanesulfonyloxyethoxy)-1-[6-(2-methylbenzoylamino)nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (0.55 g) in  
20 dimethylformamide (10 ml) is added potassium phthalimide (0.2 g), and the mixture is stirred at 110°C for one hour. The reaction solution is poured into ice-water, and the mixture is extracted with dichloromethane. The extract is washed with water, dried over magnesium sulfate, and evaporated under reduced pressure to remove the solvent. The residue is purified by silica gel  
25 column chromatography to give 7-chloro-5-(2-phthalimidoethoxy)-1-[6-(2-methylbenzoylamino)nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (0.4 g) as colorless amorphous.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.45 - 2.55 (4H, m), 2.51 (3H, s), 2.60 - 2.95 (1H,  
m), 3.70 - 4.20 (2H, m), 4.50 - 5.15 (2H, m), 6.58 (1H, d, J=8.2 Hz), 6.99 (1H, d,  
30 J=8.5 Hz), 7.20 - 8.50 (15H, m)

Example 12

To a solution of 7-chloro-5-(2-phthalimidoethoxy)-1-[6-(2-methylbenzoylamino)nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (0.26 g) in ethanol (10 ml) is added hydrazine hydrate (0.04 ml), and the mixture is refluxed for 2 hours, and cooled. Water is added to the reaction solution, and the mixture is made acidic with diluted hydrochloric acid, and washed with diethyl ether. Aqueous sodium hydroxide solution is added to the aqueous layer in order to make it basic, and the mixture is extracted with dichloromethane. The extract is washed with water, dried over magnesium sulfate, and evaporated under reduced pressure to remove the solvent. The residue is purified by silica gel column chromatography to give 7-chloro-5-(2-aminoethoxy)-1-[6-(2-methylbenzoylamino)nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (0.26 g) as colorless amorphous.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.50 - 2.60 (4H, m), 2.50 (3H, s), 2.65 - 3.20 (3H, m), 3.40 - 3.80 (2H, m), 4.45 - 5.15 (2H, m), 6.62 (1H, d,  $J=8.1$  Hz), 7.04 (1H, d,  $J=8.1$  Hz), 7.15 - 7.85 (6H, m), 8.10 - 8.50 (3H, m)

Example 13

To a solution of 7-chloro-5-(2-aminoethoxy)-1-[6-(2-methylbenzoylamino)nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (0.16 g) in methanol (3 ml) are added 37 % formaldehyde (0.3 ml) and sodium cyanoborohydride (0.06 g), and further thereto is added with stirring acetic acid (0.25 ml) at  $10^\circ\text{C}$ . The mixture is stirred at room temperature for 3 hours, and poured into ice-water. The mixture is made basic with potassium carbonate, and extracted with dichloromethane. The extract is washed with water, dried over magnesium sulfate, and evaporated under reduced pressure to remove the solvent. The residue is purified by silica gel column chromatography to give 7-chloro-5-(2-dimethylaminoethoxy)-1-[6-(2-methylbenzoylamino)nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (58 mg) as colorless amorphous.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.50 - 3.00 (13H, m), 2.50 (3H, s), 3.40 - 3.85 (2H, m), 4.45 - 5.15 (2H, m), 6.60 (1H, d,  $J=8.1$  Hz), 7.00 - 7.10 (1H, m), 7.20 -

7.90 (6H, m), 8.05 - 8.60 (3H, m)

Example 14

To a solution of 7-chloro-5-(2-aminoethoxy)-1-[6-(2-methylbenzoylamino)nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (0.14 g) in dichloromethane (5 ml) are added with stirring triethylamine (0.08 ml) and acetyl chloride (0.03 ml) under ice-cooling. The mixture is stirred at room temperature for 30 minutes, and thereto is added water, and the mixture is extracted with dichloromethane. The extract is washed with water, dried over magnesium sulfate, and evaporated under reduced pressure to remove the solvent. The residue is purified by silica gel column chromatography to give 7-chloro-5-(2-acetyl-aminoethoxy)-1-[6-(2-methylbenzoylamino)nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (85 mg) as colorless amorphous.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  : 1.60 - 2.70 (6H, m), 2.50 (3H, s), 2.70 - 3.00 (1H, m), 3.00 - 3.20 (1H, m), 3.40 - 3.80 (4H, m), 4.50 - 5.10 (2H, m), 5.95 - 6.15 (1H, m), 6.65 - 6.80 (1H, m), 7.00 - 7.20 (1H, m), 7.20 - 7.80 (6H, m), 8.05 - 8.50 (3H, m)

Example 15

To a suspension of 7-chloro-5-oxo-1-[5-(2-methylbenzoylamino)thenoyl]-2,3,4,5-tetrahydro-1H-benzazepine (1 g) in methanol (40 ml) are added molecular sieve 4A (2 g) and 40 % methylamine methanol solution (10 ml), and the mixture is refluxed for 6 hours, and cooled. To the mixture is added with stirring sodium borohydride (0.13 g) at room temperature, and the mixture is stirred at the same temperature overnight. The reaction solution is filtered on Celite, and to the filtrate is added water, and the mixture is extracted with dichloromethane. The extract is washed with water, dried over magnesium sulfate, and evaporated under reduced pressure to remove the solvent. The residue is purified by silica gel column chromatography, and recrystallized from dichloromethane-diethyl ether to give 7-chloro-5-methylamino-1-[5-(2-methylbenzoylamino)thenoyl]-2,3,4,5-tetrahydro-1H-benzazepine (0.93 g) as white powder.

- 60 -

M.p. 213 - 216°C (recrystallized from dichloromethane-diethyl ether)

Example 16

To a solution of 7-chloro-5-methylamino-1-[5-(2-methylbenzoyl-amino)thenoyl]-2,3,4,5-tetrahydro-1H-benzazepine (0.5 g) in methanol (10 ml)  
5 are added 37 % formaldehyde (0.8 ml) and sodium cyanoborohydride (0.1 g),  
and further thereto is added dropwise acetic acid (0.6 ml) at a temperature  
below 10°C. The mixture is stirred at room temperature for one hour, and  
poured into ice-water. The mixture is made basic with potassium carbonate,  
and extracted with dichloromethane. The extract is washed with water, dried  
10 over magnesium sulfate, and evaporated under reduced pressure to remove  
the solvent. The residue is purified by silica gel column chromatography to  
give 7-chloro-5-dimethylamino-1-[5-(2-methylbenzoylamino)thenoyl]-2,3,4,5-  
tetrahydro-1H-benzazepine (0.41 g) as colorless amorphous.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.20 - 2.60 (10H, m), 2.44 (3H, s), 3.15 - 3.65  
15 (2H, m), 4.00 - 5.00 (1H, m), 6.50 (2H, s), 6.90 - 7.50 (6H, m), 7.67 (1H, s), 8.73  
(1H, s)

Example 17

To a suspension of 6-(2-methylbenzoylamino)nicotinic acid (0.3 g) in  
dimethylformamide (0.5 ml) and dichloromethane (2.5 ml) is added dropwise  
20 oxazolyl chloride (0.2 ml), and the mixture is stirred at room temperature for 2  
hours. The mixture is evaporated under reduced pressure to remove the  
solvent to give 6-(2-methylbenzoylamino)nicotinoyl chloride.

To a solution of 7-chloro-5-oxo-2,3,4,5-tetrahydro-1H-benzazepine  
(0.15 g) in pyridine (5 ml) is added with stirring the above obtained 6-(2-  
25 methylbenzoylamino)nicotinoyl chloride, and the mixture is stirred at room  
temperature for 4 hours. Water is added to the reaction solution, and the  
mixture is extracted with ethyl acetate. The extract is washed with water, dried  
over magnesium sulfate, and evaporated under reduced pressure to remove  
the solvent. The residue is purified by silica gel column chromatography to  
30 give 7-chloro-5-oxo-1-[6-(2-methylbenzoylamino)nicotinoyl]-2,3,4,5-tetrahydro-

- 61 -

1H-benzazepine (0.16 g) as colorless amorphous.

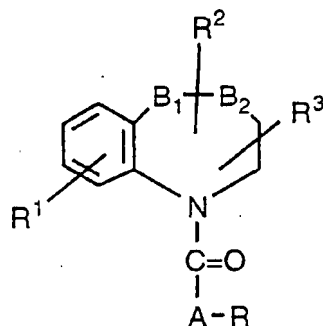
<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 2.0 - 2.4 (2H, m), 2.50 (3H, s), 2.89 (2H, t, J=6.2 Hz), 3.2 - 5.0 (2H, br), 6.72 (1H, d, J=8.4 Hz), 7.20 - 7.51 (5H, m), 7.60 (1H, dd, J=2.3, 8.7 Hz), 7.86 (1H, d, J=2.5 Hz), 8.09 (1H, d, J=1.7 Hz), 8.24 (1H, d, J=8.7 Hz), 8.50 (1H, s)

5

Examples 18 - 148

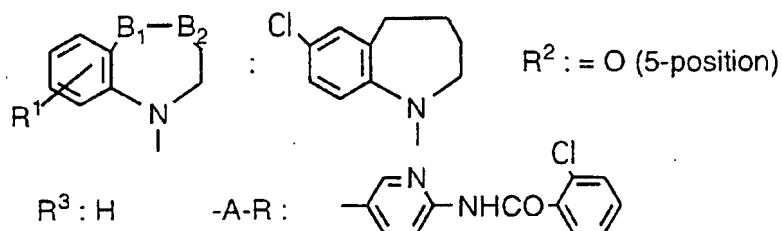
Using the suitable starting compounds, the following compounds listed in Table 1 are obtained in the same manner as in Examples 1 and 17. Table 2 shows the NMR analysis of these compounds.

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Table 1

## Example 18

Structure:



Crystalline form: White powder

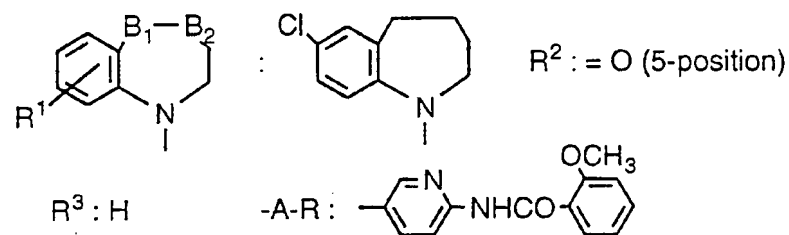
Recrystallization solvent: Methanol

Melting point: 172 - 174.5°C

Form: Free

## Example 19

Structure:



Crystalline form: White powder

Recrystallization solvent: Dichloromethane-diethyl ether

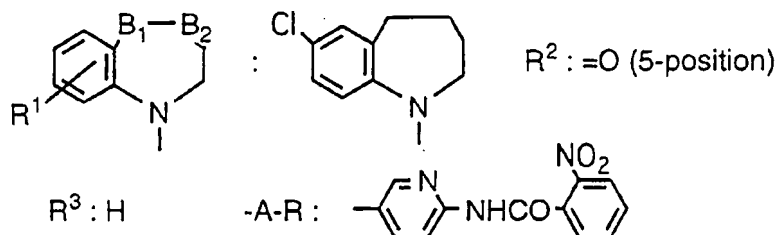
Melting point: 234 - 237°C

Form: Free



## Example 20

Structure:



Crystalline form: White powder

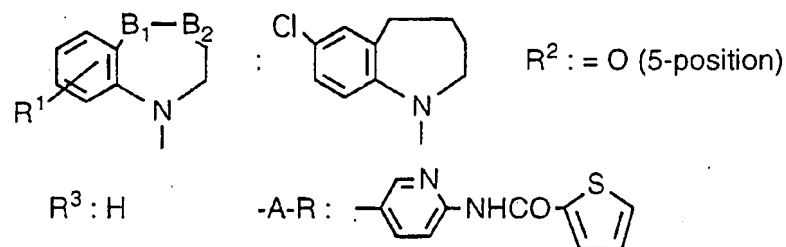
Recrystallization solvent: Dichloromethane-diethyl ether

Melting point: 194 - 196°C

From: Free

## Example 21

Structure



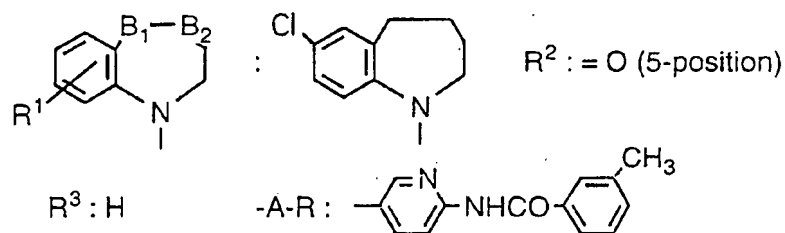
Crystalline form: White powder

Recrystallization solvent: Methanol

Melting point: 206 - 207°C

From: Free

## Example 22



Crystalline form: White powder

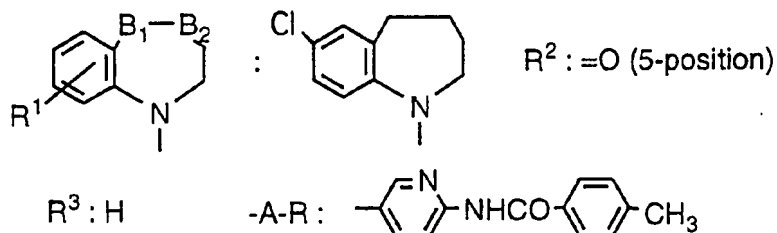
Recrystallization solvent: Methanol

Melting point: 169.5 - 171.5°C

From: Free

## Example 23

Structure:



Crystalline form: White powder

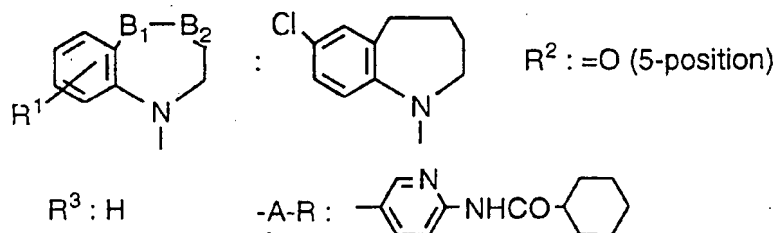
Recrystallization solvent: Methanol

Melting point: 169.5- 172.5°C

Form: Free

## Example 24

Structure:



Crystalline form: White powder

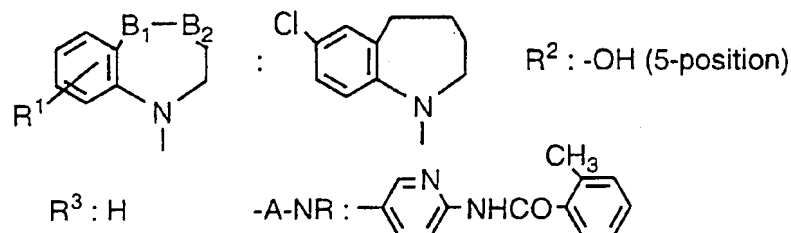
Recrystallization solvent: Methanol

Melting point: 173 - 174°C

Form: Free

## Example 25

Structure:



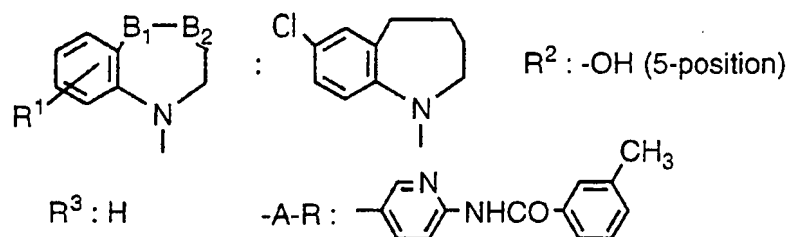
Crystalline form: Colorless amorphous

NMR analysis: 1)

Form: Free

## Example 26

Structure:



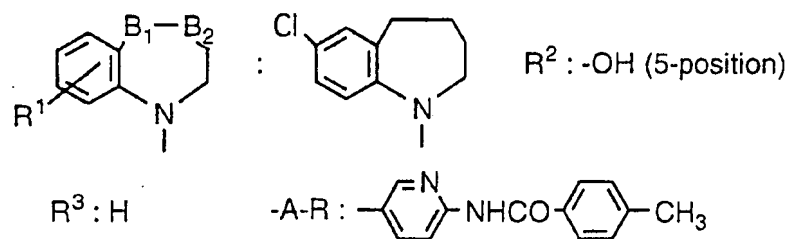
Crystalline form: Colorless amorphous

NMR analysis: 2)

Form: Free

## Example 27

Structure:



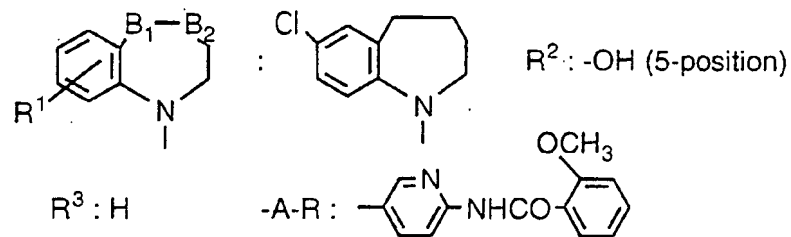
Crystalline form: Colorless amorphous

NMR analysis: 3)

Form: Free

## Example 28

Structure:



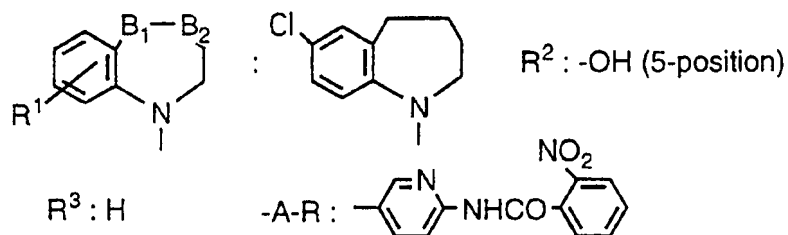
Crystalline form: Colorless amorphous

NMR analysis 4)

Form: Free

## Example 29

Structure:



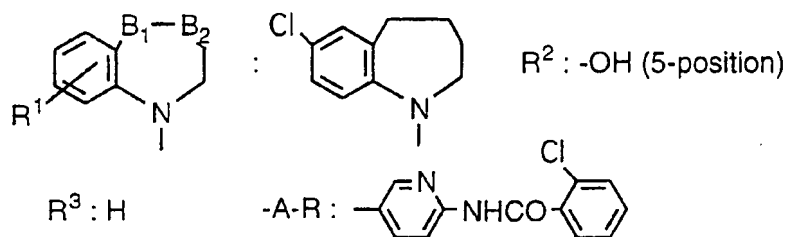
Crystalline form: Colorless amorphous

NMR analysis: 5)

Form: Free

## Example 30

Structure:



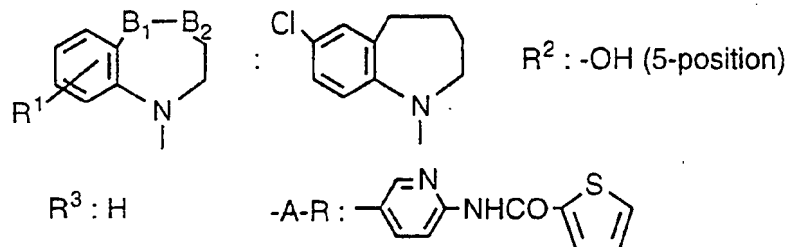
Crystalline form: Colorless amorphous

NMR analysis: 6)

Form: Free

## Example 31

Structure:



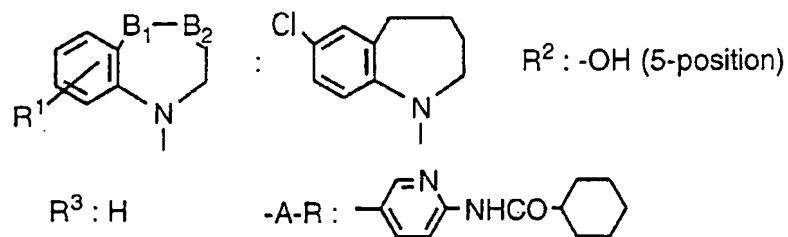
Crystalline form: Colorless amorphous

NMR analysis 7)

Form: Free

## Example 32

Structure:



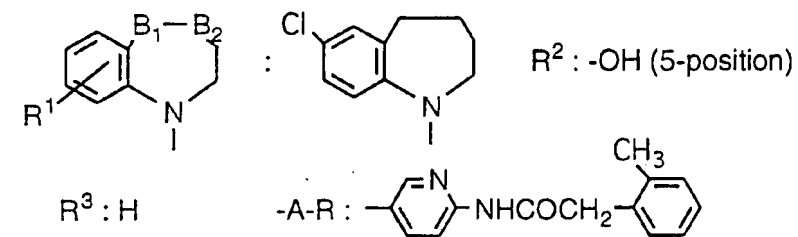
Crystalline form: Colorless amorphous

NMR analysis: 8)

Form: Free

## Example 33

Structure:



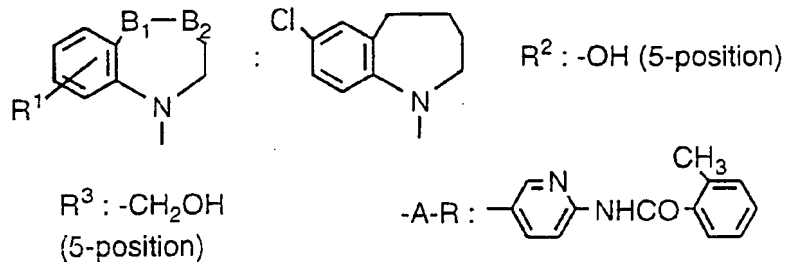
Crystalline form: Colorless amorphous

NMR analysis: 9)

Form: Free

## Example 34

Structure:



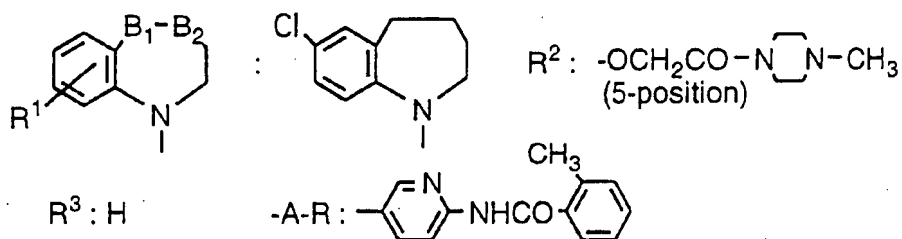
Crystalline form: Colorless amorphous

NMR analysis 10)

Form: Free

## Example 35

Structure:



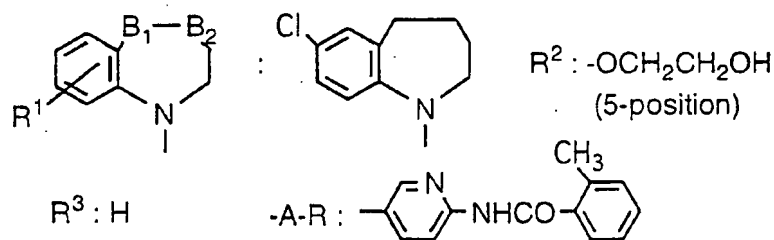
Crystalline form: Colorless amorphous

NMR analysis: 11)

Form: Free

## Example 36

Structure:



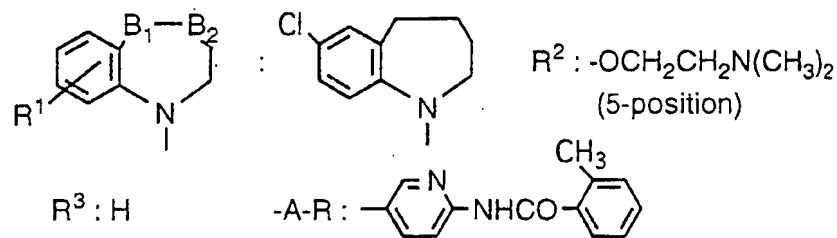
Crystalline form: Colorless amorphous

NMR analysis: 12)

Form: Free

## Example 37

Structure:



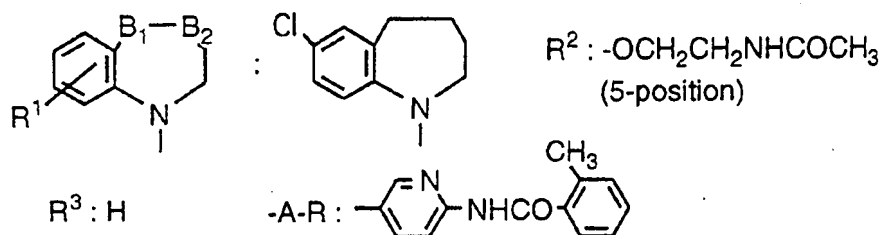
Crystalline form: Colorless amorphous

NMR analysis 13)

Form: Free

## Example 38

Structure:



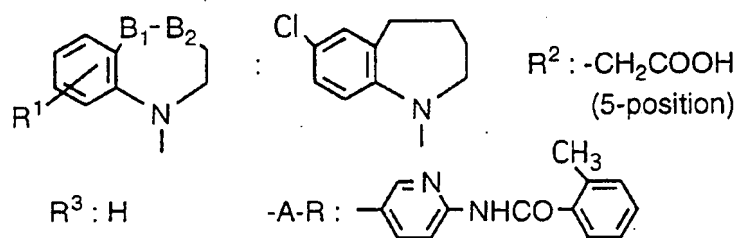
Crystalline form: Colorless amorphous

NMR analysis: 14)

Form: Free

## Example 39

Structure:



Crystalline form: White powder

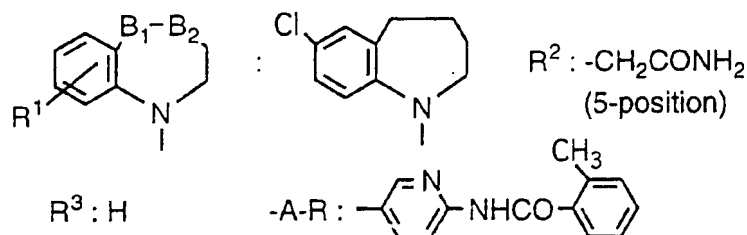
Recrystallization solvent: Dichloromethane-diethyl ether

Melting point: 187 - 190°C

Form: Free

## Example 40

Structure:



Crystalline form: White powder

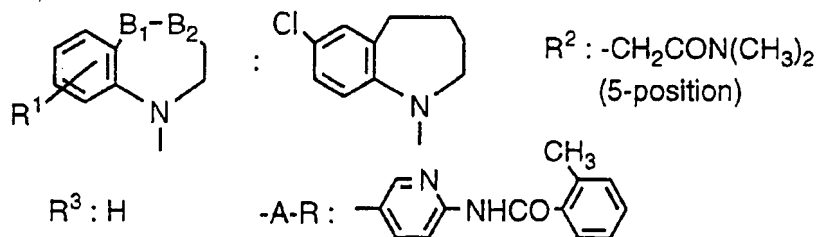
Recrystallization solvent: Dichloromethane-diethyl ether

Melting point: 141 - 144°C

Form: Free

## Example 41

Structure:



Crystalline form: White powder

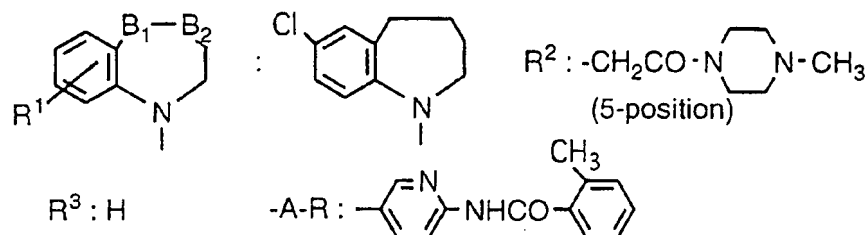
Recrystallization solvent: Dichloromethane-diethyl ether

Melting point: 197 - 198.5°C

Form: Free

## Example 42

Structure:



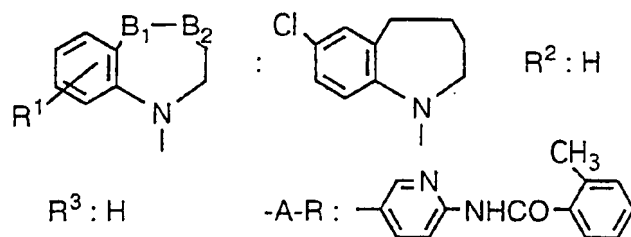
Crystalline form: Colorless amorphous

NMR analysis: 15)

Form: Free

## Example 43

Structure:



Crystalline form: White powder

Recrystallization solvent: Dichloromethane-diethyl ether

Melting point: 194 - 197°C

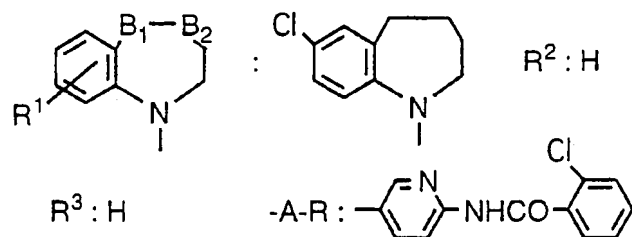
Form: Free



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Example 44

Structure:



Crystalline form: White powder

Recrystallization solvent: Dichloromethane-diethyl ether

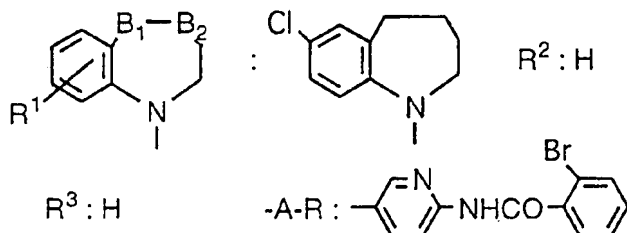
Melting point: 193 - 195°C

Form: Free

---

Example 45

Structure:



Crystalline form: Yellow powder

Recrystallization solvent: Dichloromethane-diethyl ether

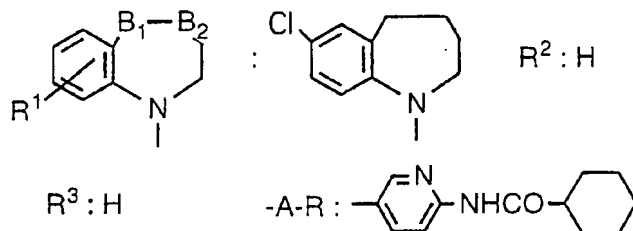
Melting point: 205.5 - 208.5°C

Form: Free

---

Example 46

Structure:



Crystalline form: White powder

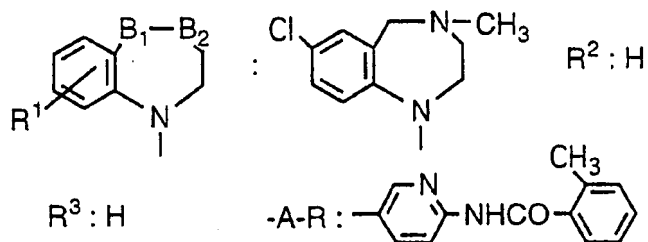
Recrystallization solvent: Dichloromethane-diethyl ether

Melting point: 182 - 183.5°C

Form: Free

## Example 47

Structure:



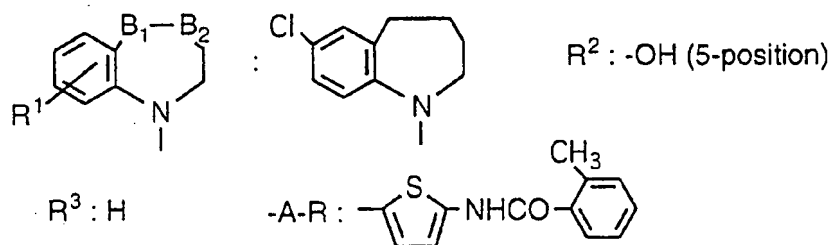
Crystalline form: Colorless amorphous

NMR analysis: 16)

Form: Free

## Example 48

Structure:



Crystalline form: White powder

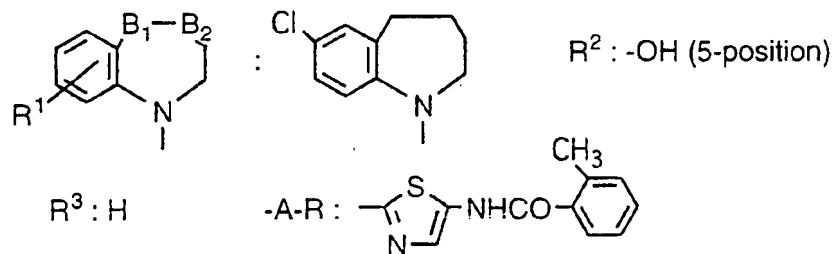
Recrystallization solvent: Dichloromethane-diethyl ether

Melting point: 238.5 - 240°C

Form: Free

## Example 49

Structure:



Crystalline form: White powder

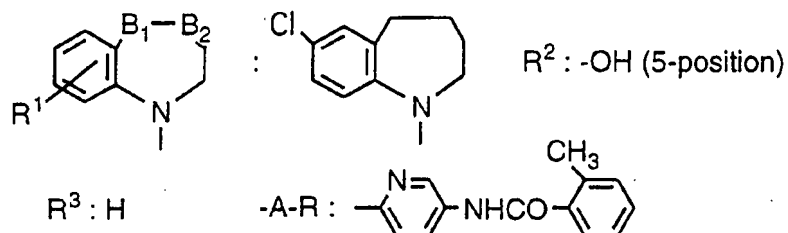
Recrystallization solvent: Dichloromethane-diethyl ether

Melting point: 235 - 237°C

Form: Free

## Example 50

Structure:



Crystalline form: White powder

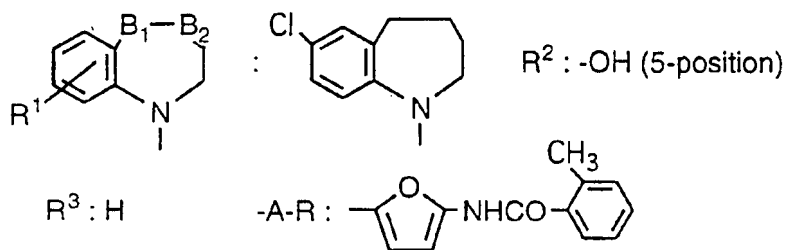
Recrystallization solvent: Dichloromethane-diethyl ether

Melting point: 196 - 199°C

Form: Free

## Example 51

Structure:



Crystalline form: White powder

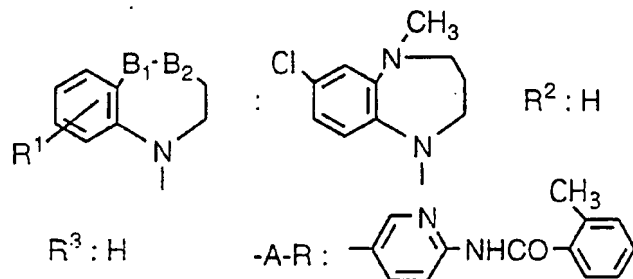
Recrystallization solvent: Dichloromethane-diethyl ether

Melting point: 180 - 183°C

Form: Free

## Example 52

Structure:



Crystalline form: White powder

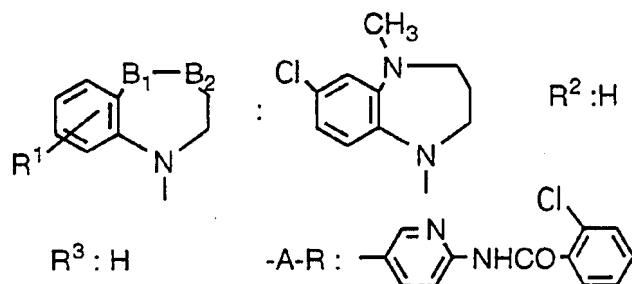
Recrystallization solvent: Dichloromethane-diethyl ether

Melting point: 167 - 169.5°C

Form: Free

## Example 53

Structure:



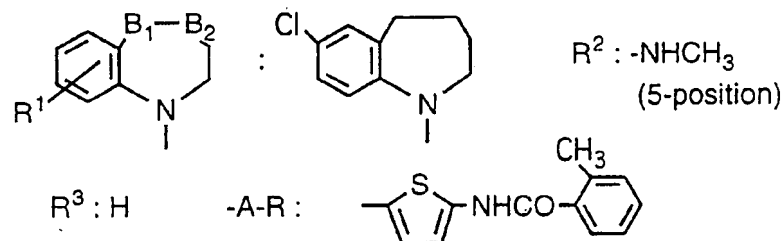
Crystalline form: Colorless amorphous

NMR analysis: 17)

Form: Free

## Example 54

Structure:



Crystalline form: White powder

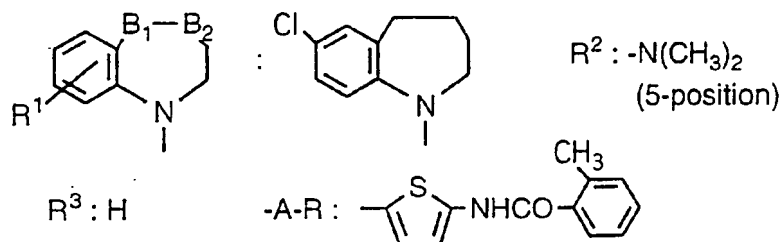
Recrystallization solvent: Dichloromethane-diethyl ether

Melting point: 213 - 216°C

Form: Free

## Example 55

Structure:



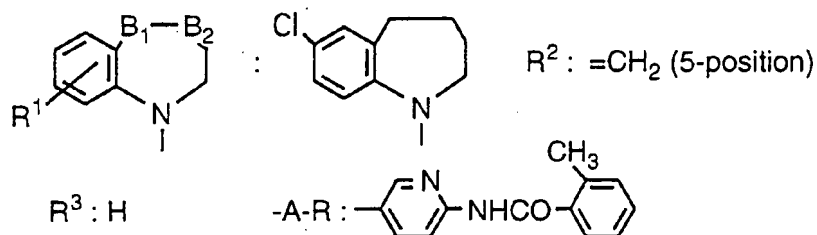
Crystalline form: Colorless amorphous

NMR analysis: 18)

Form: Free

## Example 56

Structure:



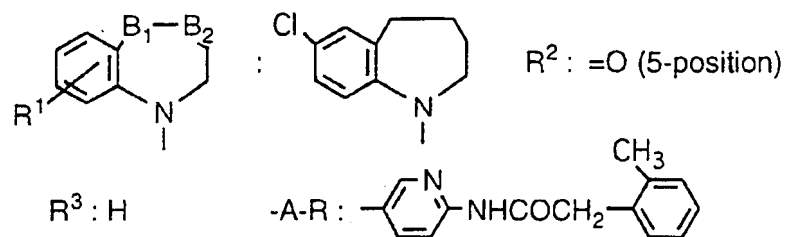
Crystalline form: Yellow amorphous

NMR analysis: 19)

Form: Free

## Example 57

Structure:



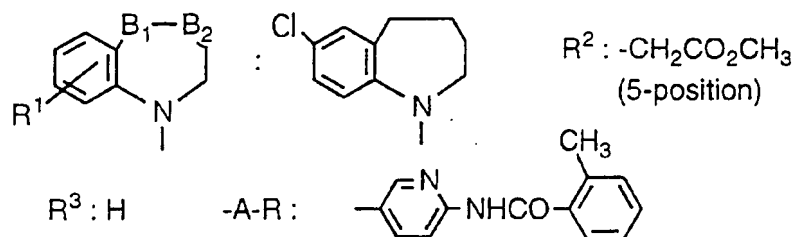
Crystalline form: Colorless amorphous

NMR analysis: 20)

Form: Free

## Example 58

Structure:



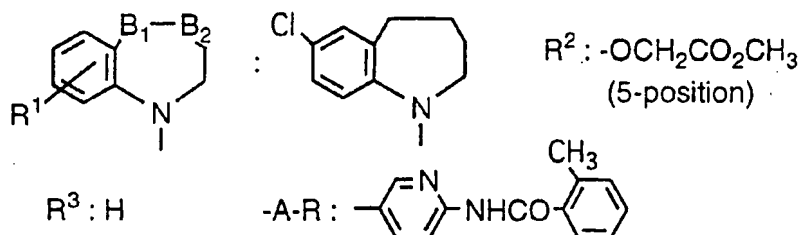
Crystalline form: White powder

NMR analysis: 21)

Form: Free

## Example 59

Structure:



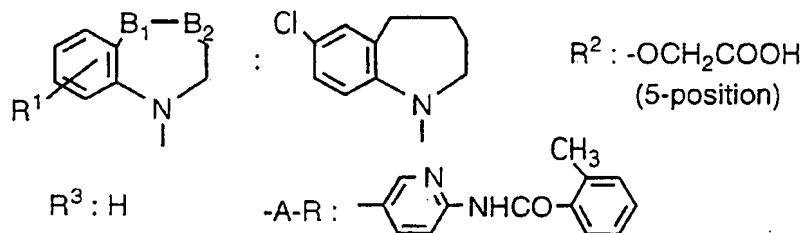
Crystalline form: White powder

Recrystallization solvent: Dichloromethane-diethyl ether

Melting point: 182 - 184°C Form: Free

## Example 60

Structure:



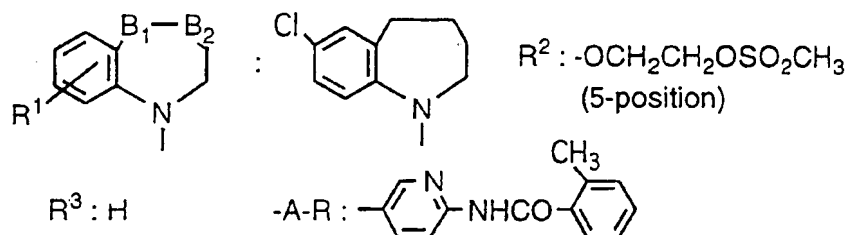
Crystalline form: White powder

Recrystallization solvent: Diethyl ether

Melting point: 220 - 222°C Form: Free

## Example 61

Structure:



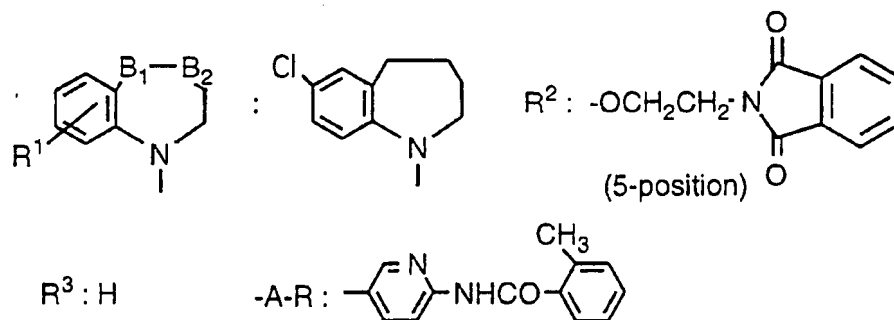
Crystalline form: Colorless amorphous

NMR analysis: 22)

Form: Free

## Example 62

Structure:



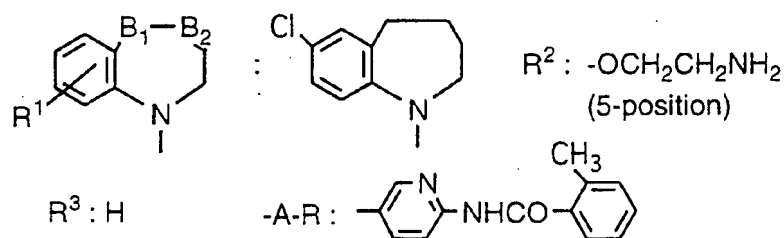
Crystalline form: Colorless amorphous

NMR analysis: 23)

Form: Free

## Example 63

Structure:



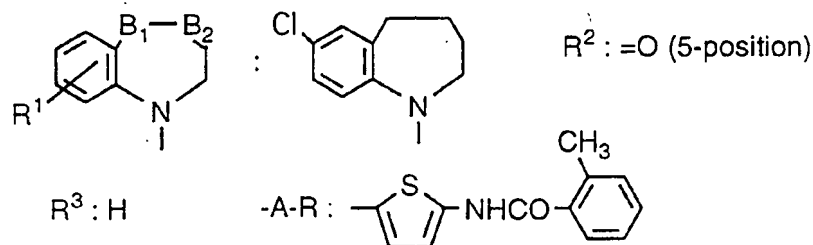
Crystalline form: Colorless amorphous

NMR analysis: 24)

Form: Free

## Example 64

Structure:



Crystalline form: White powder

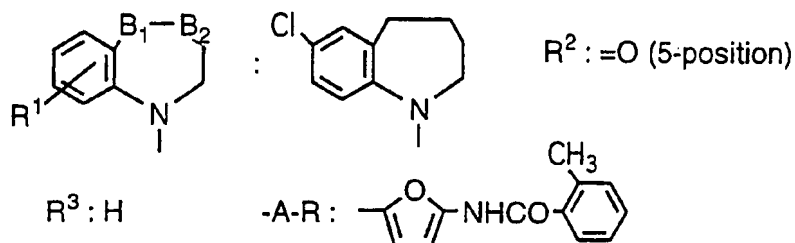
Recrystallization solvent: Dichloromethane-diethyl ether

Melting point: 207 - 210°C

Form: Free

## Example 65

Structure:



Crystalline form: Yellow powder

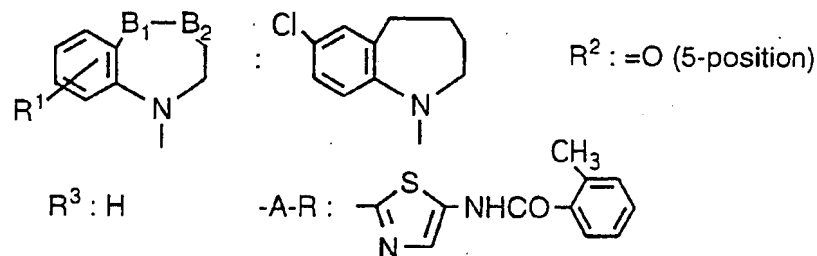
Recrystallization solvent: Dichloromethane-diethyl ether

Melting point: 225 - 228°C

Form: Free

## Example 66

Structure:



Crystalline form: Yellow powder

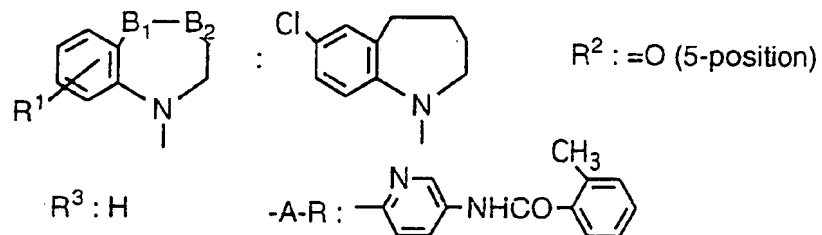
Recrystallization solvent: Dichloromethane-diethyl ether

Melting point: 182.5 - 185.5°C

Form: Free

## Example 67

Structure:



Crystalline form: White powder

Recrystallization solvent: Dichloromethane-diethyl ether

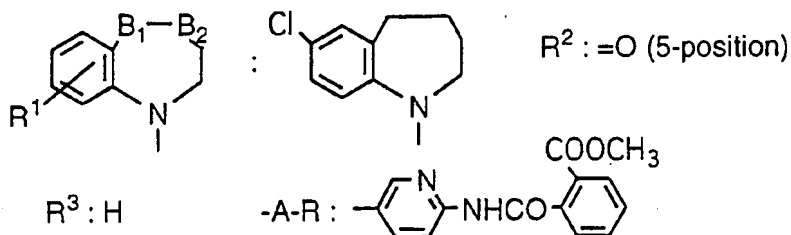
Melting point: 183 - 184.5°C

Form: Free



## Example 68

Structure:



Crystalline form: White powder

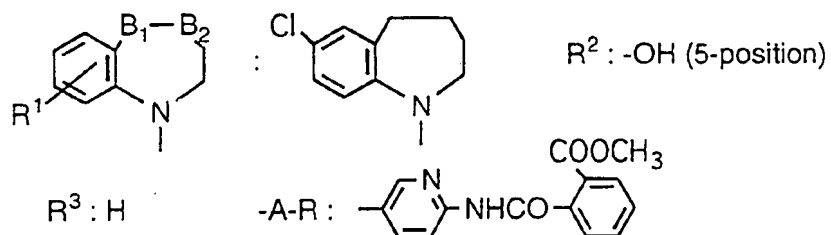
Recrystallization solvent: Dichloromethane-diethyl ether

Melting point: 160 - 162°C

Form: Free

## Example 69

Structure:



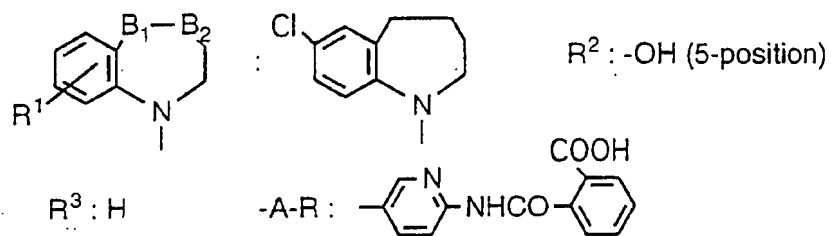
Crystalline form: Colorless amorphous

NMR analysis: 25)

Form: Free

## Example 70

Structure:



Crystalline form: White powder

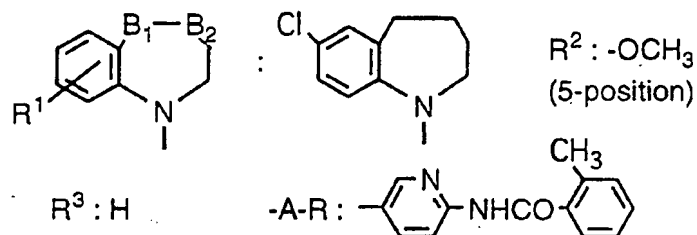
Recrystallization solvent: Dichloromethane - methanol

Melting point: 153 - 155°C

Form: Free

## Example 71

Structure:



Crystalline form: White powder

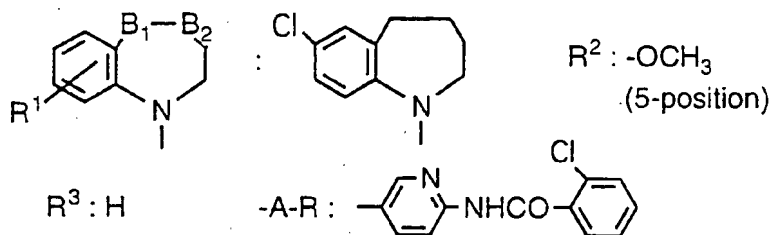
Recrystallization solvent: Dichloromethane-diethyl ether

Melting point: 171 - 174°C

Form: Free

## Example 72

Structure:



Crystalline form: White powder

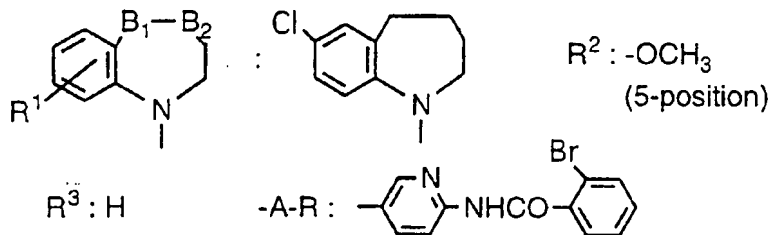
Recrystallization solvent: Dichloromethane-diethyl ether

Melting Point: 176 - 178°C

Form: Free

## Example 73

Structure:



Crystalline form: White powder

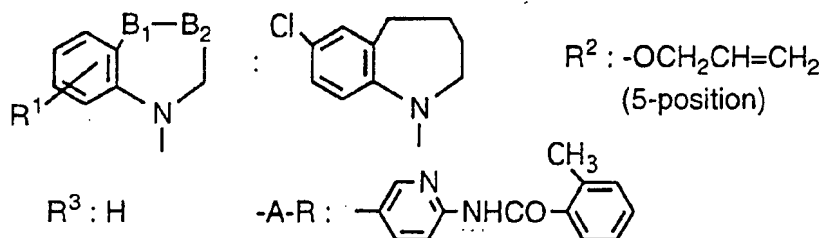
Recrystallization solvent: Dichloromethane-diethyl ether

Melting point: 184 - 186°C

Form: Free

## Example 74

Structure:



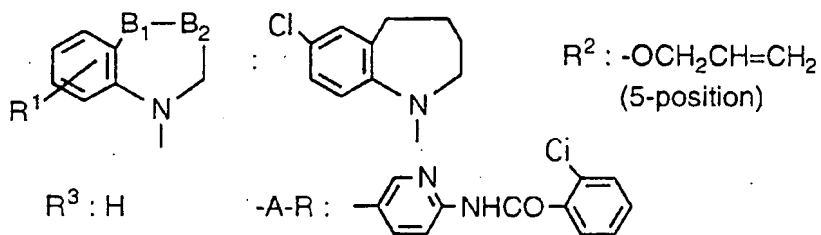
Crystalline form: White powder

NMR analysis: 54)

Form: Free

## Example 75

Structure:



Crystalline form: White powder

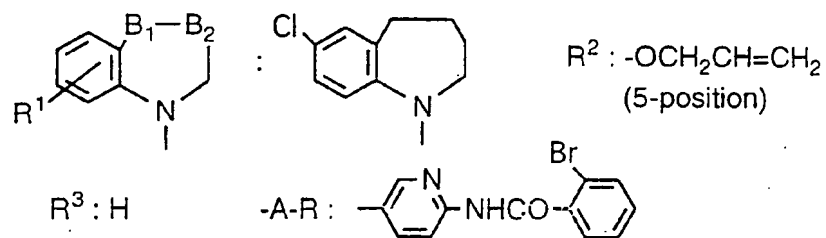
Recrystallization solvent: Dichloromethane-diethyl ether

Melting Point: 152 - 154°C

Form: Free

## Example 76

Structure:



Crystalline form: White powder

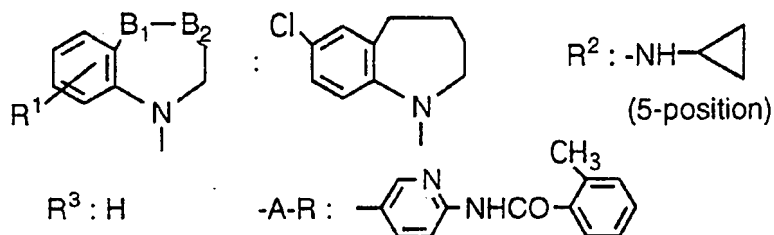
Recrystallization solvent: Dichloromethane-diethyl ether

Melting point: 183 - 186°C

Form: Free

## Example 77

Structure:



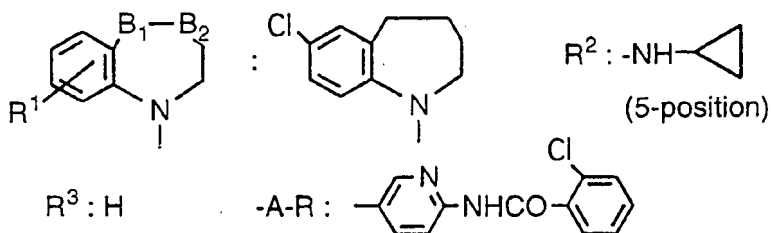
Crystalline form: White powder

NMR analysis: 55)

Form: Free

## Example 78

Structure:



Crystalline form: White powder

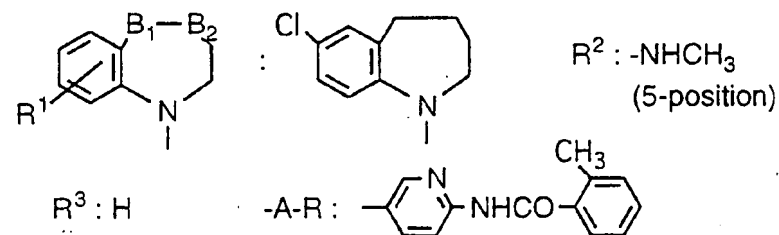
Recrystallization solvent: Dichloromethane-diethyl ether

Melting Point: 162 - 165°C

Form: Free

## Example 79

Structure:



Crystalline form: White powder

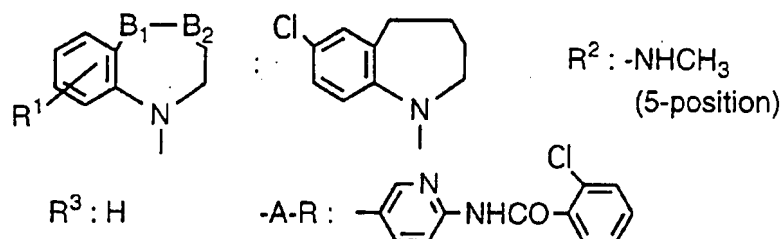
Recrystallization solvent: Dichloromethane-diethyl ether

Melting point: 172 - 175°C

Form: Free

## Example 80

Structure:



Crystalline form: White powder

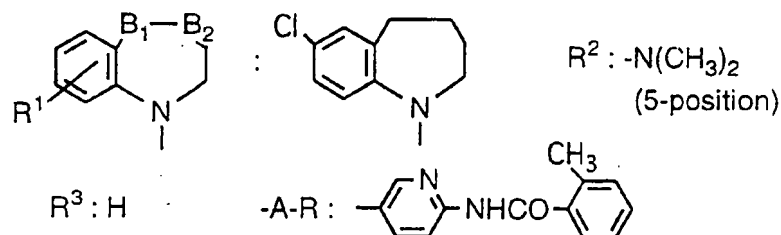
Recrystallization solvent: Dichloromethane-diethyl ether

Melting point: 162 - 165°C

Form: Free

## Example 81

Structure:



Crystalline form: White powder

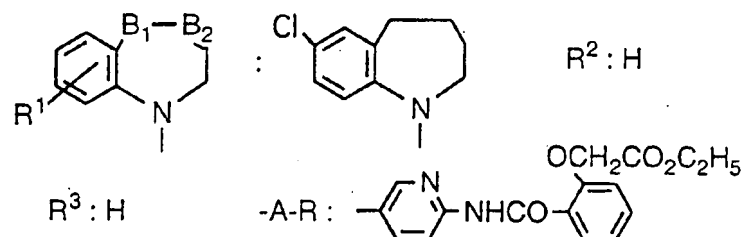
Recrystallization solvent: Dichloromethane-diethyl ether

Melting Point: 200 - 202°C

Form: Free

## Example 82

Structure:



Crystalline form: White powder

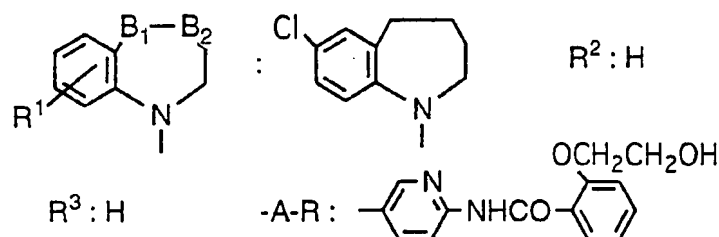
Recrystallization solvent: Dichloromethane-diethyl ether

Melting point: 187 - 189°C

Form: Free

## Example 83

Structure:



Crystalline form: White powder

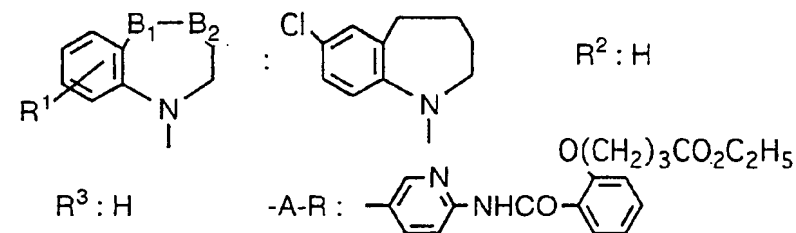
Recrystallization solvent: Dichloromethane-diethyl ether

Melting point: 213 - 216°C

Form: Free

## Example 84

Structure:



Crystalline form: White powder

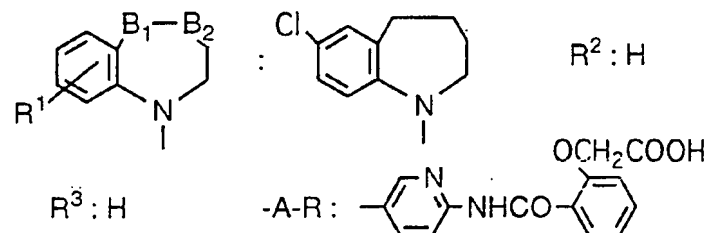
Recrystallization solvent: Dichloromethane-diethyl ether

Melting Point: 122 - 125°C

Form: Free

## Example 85

Structure:



Crystalline form: White powder

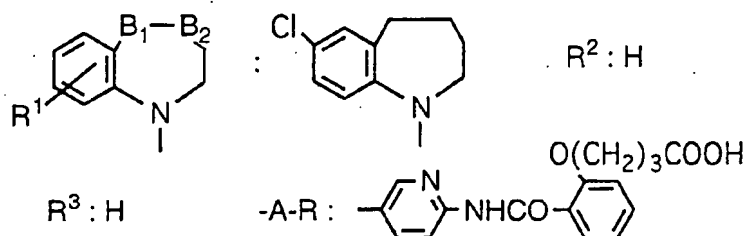
Recrystallization solvent: Dichloromethane-diethyl ether

Melting point: 155 - 157°C

Form: Free

## Example 86

Structure:



Crystalline form: White powder

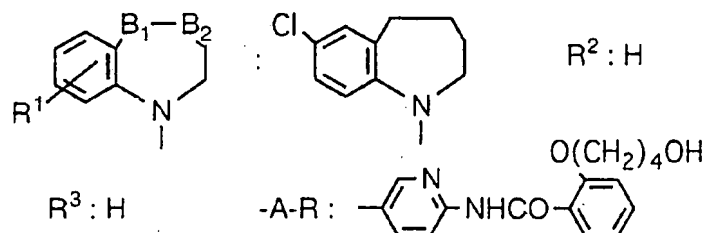
Recrystallization solvent: Dichloromethane-diethyl ether

Melting point: 182 - 184°C

Form: Free

## Example 87

Structure:



Crystalline form: White powder

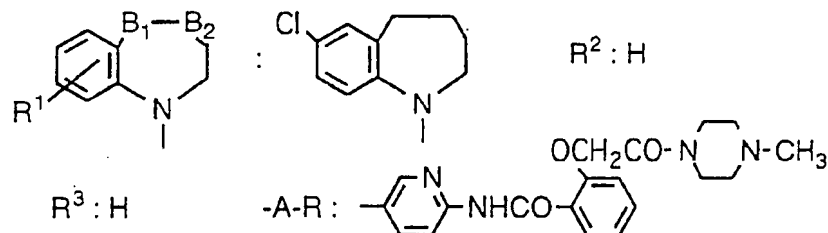
Recrystallization solvent: Dichloromethane-diethyl ether

Melting Point: 157 - 158.5°C

Form: Free

## Example 88

Structure:



Crystalline form: White powder

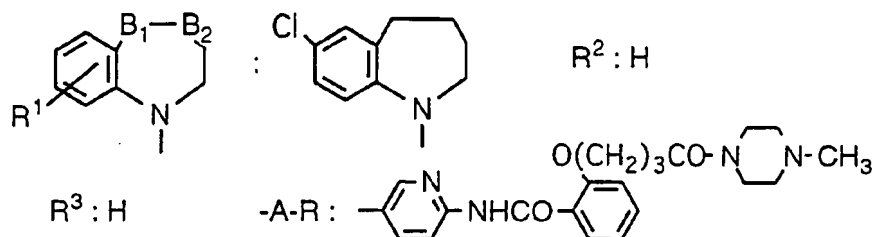
Recrystallization solvent: Dichloromethane-diethyl ether

Melting point: 111 - 114°C

Form: Free

## Example 89

Structure:



Crystalline form: White powder

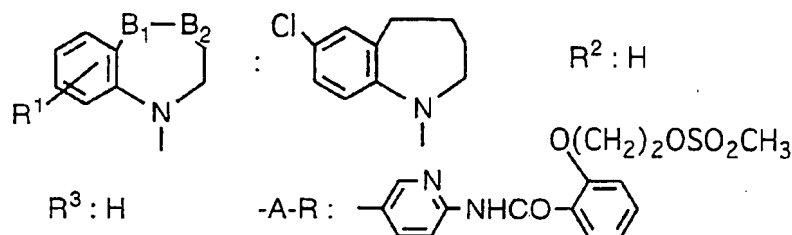
Recrystallization solvent: Dichloromethane-diethyl ether

Melting point: 127 - 130°C

Form: Free

## Example 90

Structure:



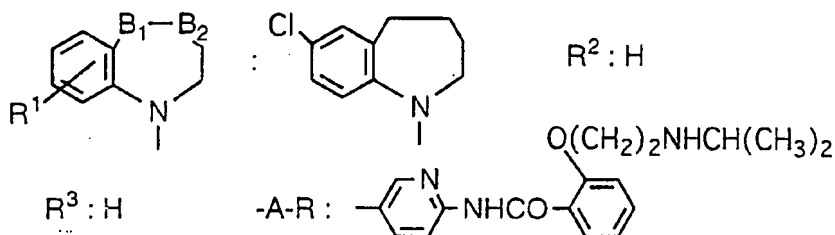
Crystalline form: White powder

NMR analysis: 26)

Form: Free

## Example 91

Structure:



Crystalline form: White powder

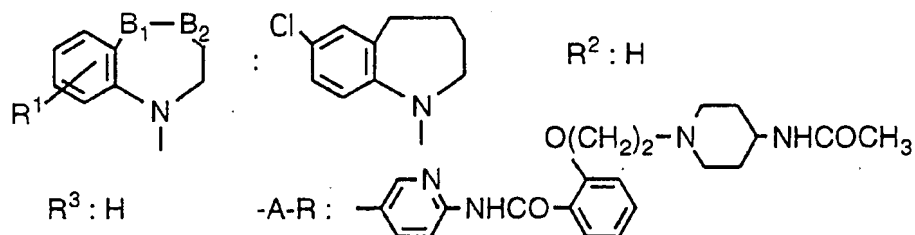
NMR analysis: 27)

Form: 2 HCl



## Example 92

Structure:



Crystalline form: White powder

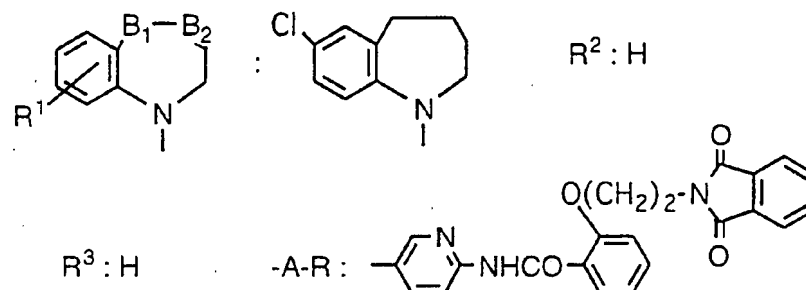
Recrystallization solvent: Dichloromethane-diethyl ether

Melting point: 159 - 162°C

Form: Free

## Example 93

Structure:



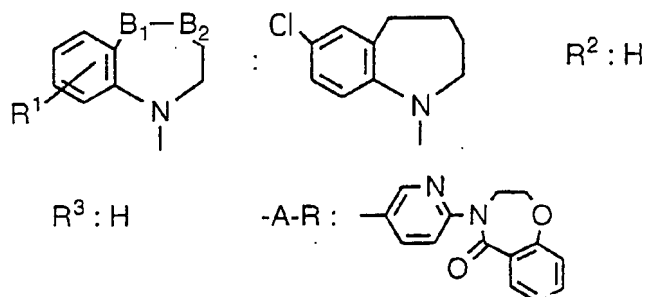
Crystalline form: White powder

NMR analysis: 28)

Form: Free

## Example 94

Structure:



Crystalline form: White powder

Recrystallization solvent: Ethyl acetate

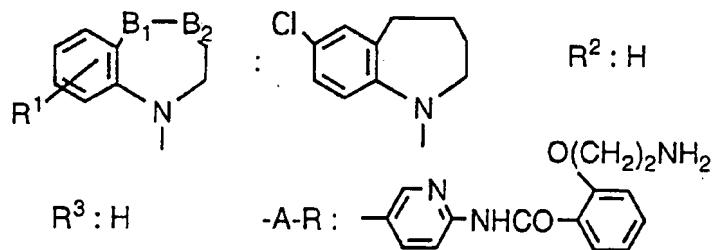
Melting point: 176 - 179°C

Form: Free

\*) This compound is obtained only by the process of Example 17.

## Example 95

Structure:

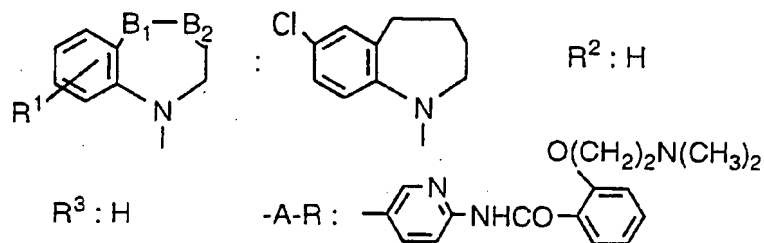


Crystalline form: White powder

NMR analysis: 29) Form: Free

## Example 96

Structure:

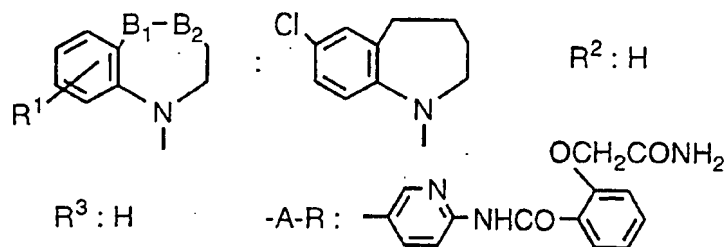


Crystalline form: White powder

NMR analysis: 30) Form: 2 HCl

## Example 97

Structure:



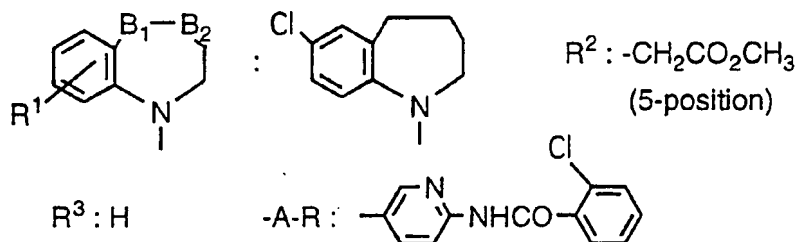
Crystalline form: White powder

Recrystallization solvent: Dichloromethane-diethyl ether

Melting point: 204 - 207°C Form: Free

## Example 98

Structure:



Crystalline form: White powder

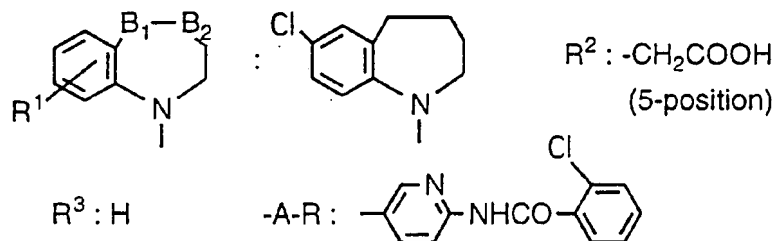
Recrystallization solvent: Dichloromethane-diethyl ether

Melting point: 167 - 170°C

Form: Free

## Example 99

Structure:



Crystalline form: White powder

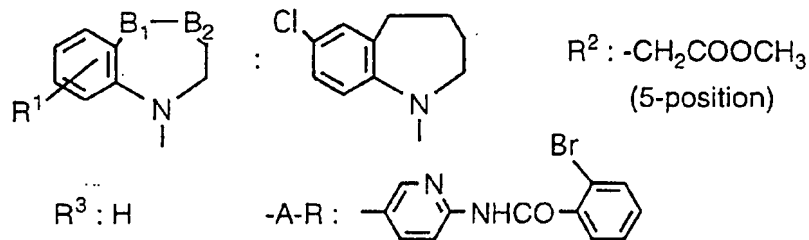
Recrystallization solvent: Dichloromethane-diethyl ether

Melting Point: 224 - 227°C

Form: Free

## Example 100

Structure:



Crystalline form: White powder

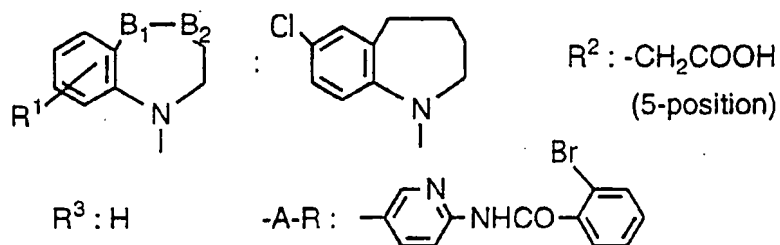
Recrystallization solvent: Dichloromethane-diethyl ether

Melting point: 185 - 188°C

Form: Free

## Example 101

Structure:



Crystalline form: White powder

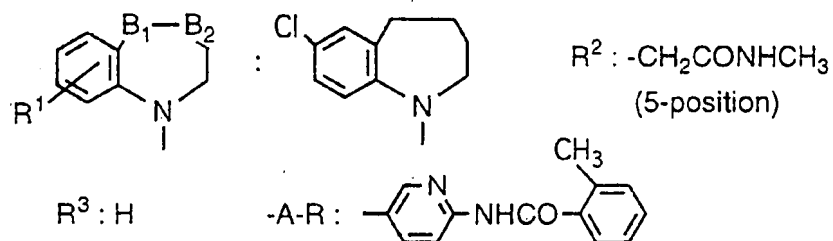
Recrystallization solvent: Ethyl acetate - diethyl ether

Melting point: 221 - 223°C

Form: Free

## Example 102

Structure:



Crystalline form: White powder

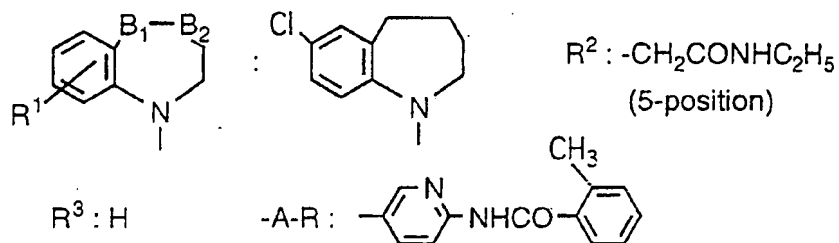
Recrystallization solvent: Dichloromethane-diethyl ether

Melting Point: 134 - 137°C

Form: Free

## Example 103

Structure:



Crystalline form: White powder

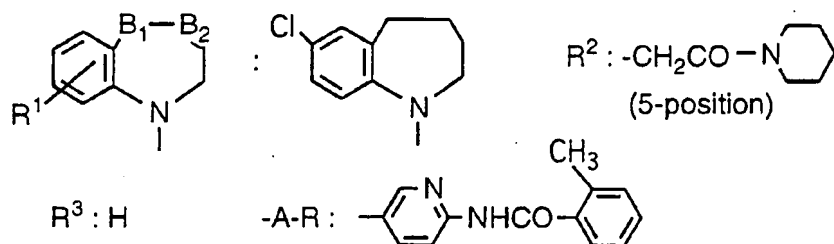
Recrystallization solvent: Dichloromethane-diethyl ether

Melting point: 196 - 199°C

Form: Free

## Example 104

Structure:



Crystalline form: White powder

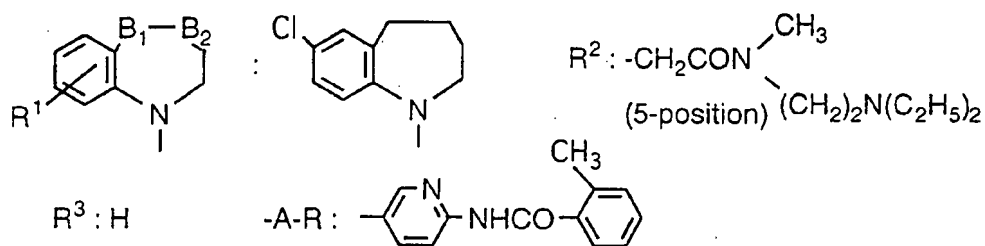
Recrystallization solvent: Dichloromethane-diethyl ether

Melting point: 254 - 256°C

Form: Free

## Example 105

Structure:



Crystalline form: White powder

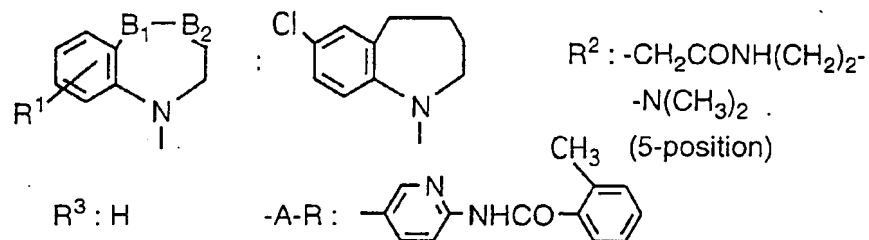
Recrystallization solvent: Dichloromethane-diethyl ether

Melting Point: 156 - 158°C

Form: Free

## Example 106

Structure:



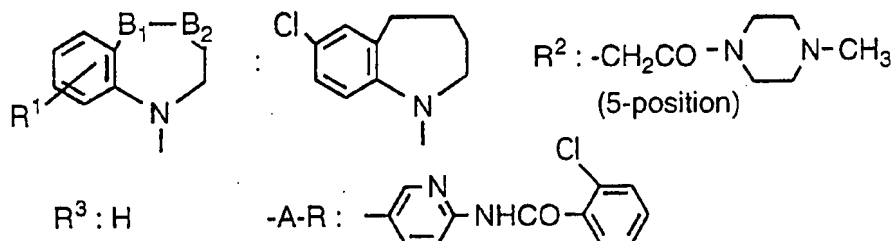
Crystalline form: Colorless amorphous

NMR analysis: 31)

Form: Free

## Example 107

Structure:



Crystalline form: White powder

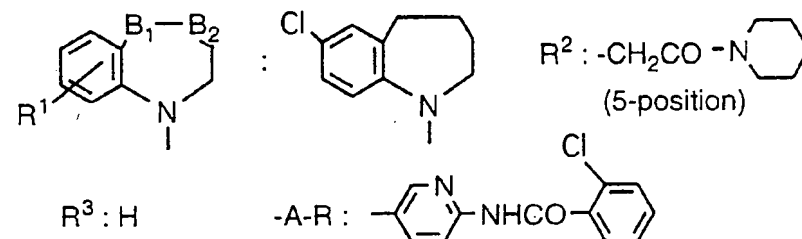
Recrystallization solvent: Dichloromethane-diethyl ether

Melting point: 222 - 225°C

Form: Free

## Example 108

Structure:



Crystalline form: White powder

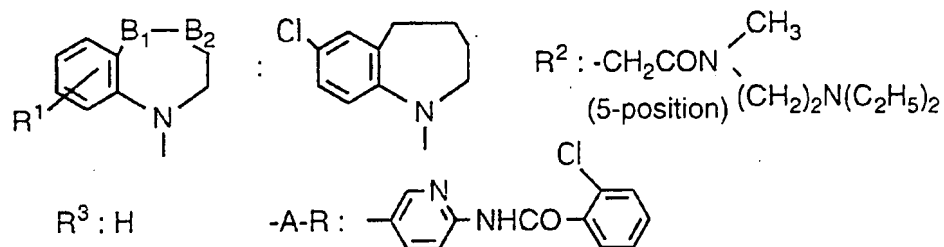
Recrystallization solvent: Dichloromethane-diethyl ether

Melting Point: 229 - 232°C

Form: Free

## Example 109

Structure:



Crystalline form: White powder

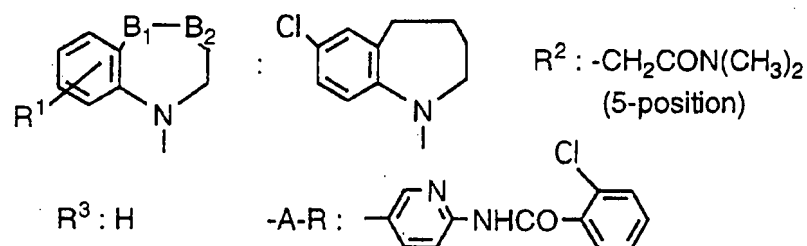
Recrystallization solvent: Dichloromethane-diethyl ether

Melting point: 152 - 154°C

Form: Free

## Example 110

Structure:



Crystalline form: White powder

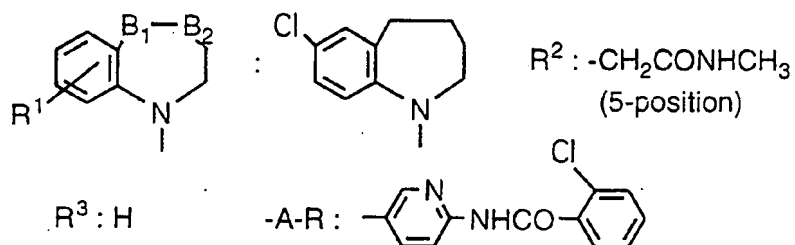
Recrystallization solvent: Dichloromethane-diethyl ether

Melting point: 216 - 217°C

Form: Free

## Example 111

Structure:



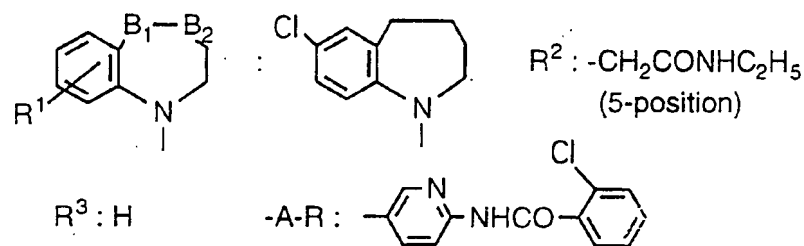
Crystalline form: White powder

NMR analysis: 56)

Form: Free

## Example 112

Structure:



Crystalline form: White powder

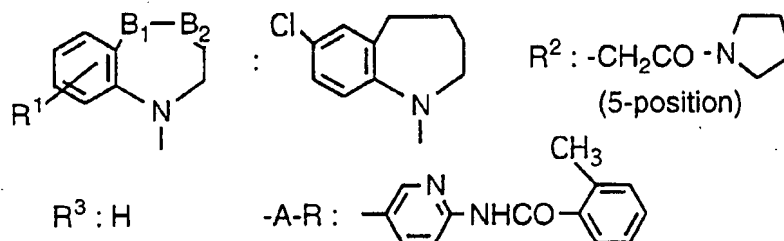
Recrystallization solvent: Dichloromethane-diethyl ether

Melting point: 203 - 205°C

Form: Free

## Example 113

Structure:



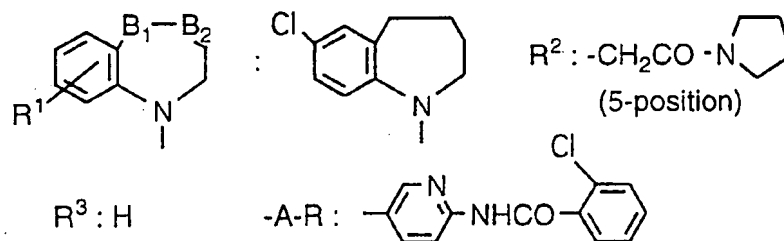
Crystalline form: White powder

Recrystallization solvent: Dichloromethane-diethyl ether

Melting point: 191 - 193.5°C Form: Free

## Example 114

Structure:



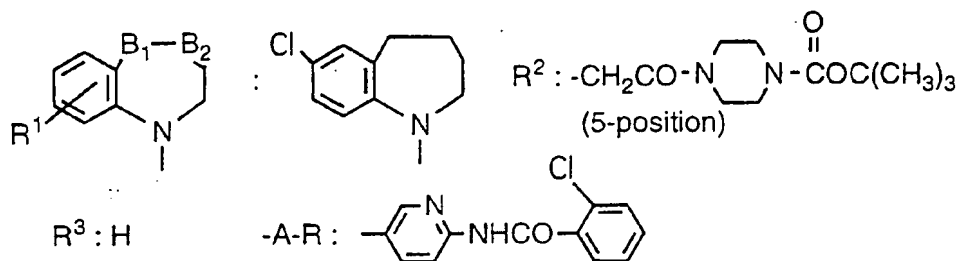
Crystalline form: White powder

Recrystallization solvent: Dichloromethane-diethyl ether

Melting Point: 191 - 193°C Form: Free

## Example 115

Structure:



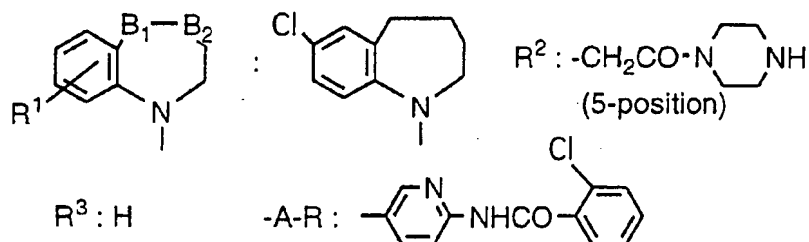
Crystalline form: Colorless amorphous

NMR analysis: 32) Form: Free



## Example 116

Structure:



Crystalline form: White powder

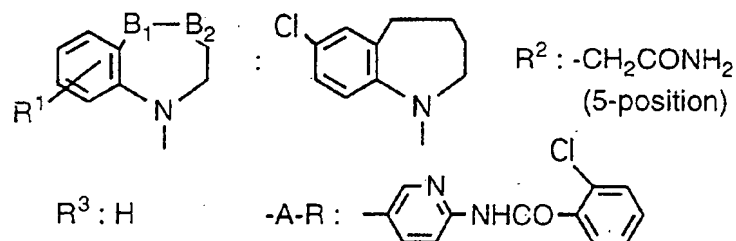
Recrystallization solvent: Ethyl acetate - diethyl ether

Melting point: 157 - 160°C

Form: Free

## Example 117

Structure:



Crystalline form: White powder

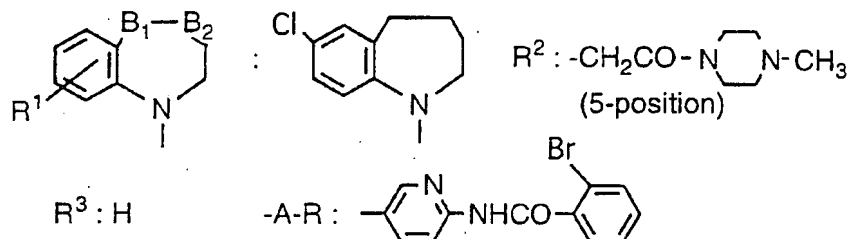
Recrystallization solvent: Dichloromethane-diethyl ether

Melting Point: 242 - 244°C

Form: Free

## Example 118

Structure:



Crystalline form: White powder

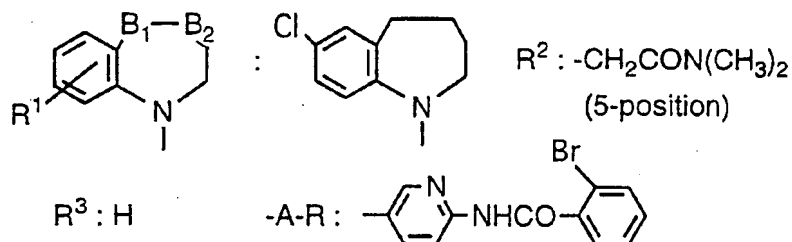
Recrystallization solvent: Dichloromethane-diethyl ether

Melting point: 223 - 225.5°C

Form: Free

## Example 119

Structure:



Crystalline form: White powder

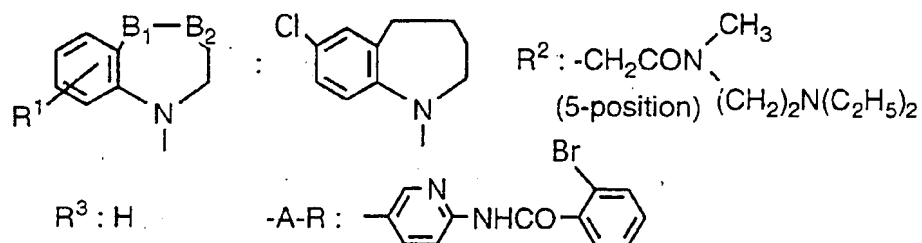
Recrystallization solvent: Dichloromethane-diethyl ether

Melting point: 224 - 225°C

Form: Free

## Example 120

Structure:



Crystalline form: White powder

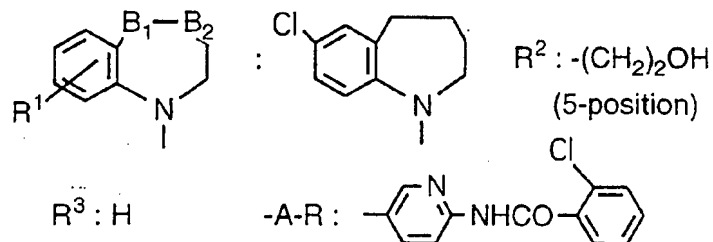
Recrystallization solvent: Dichloromethane-diethyl ether

Melting Point: 145 - 147°C

Form: Free

## Example 121

Structure:



Crystalline form: White powder

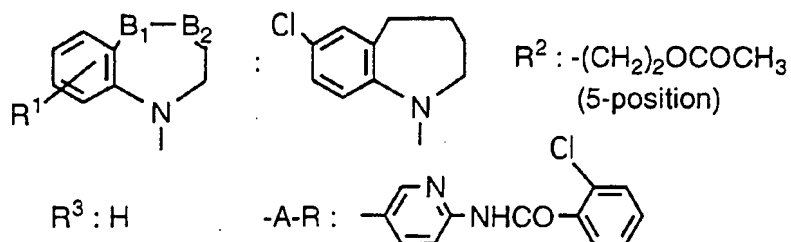
Recrystallization solvent: Dichloromethane-diethyl ether

Melting point: 161 - 163°C

Form: Free

## Example 122

Structure:



Crystalline form: White powder

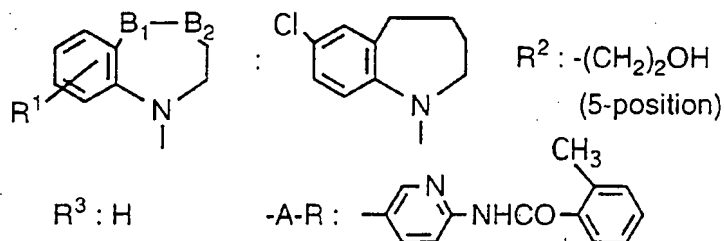
Recrystallization solvent: Dichloromethane-diethyl ether

Melting point: 151 - 153°C

Form: Free

## Example 123

Structure:



Crystalline form: White powder

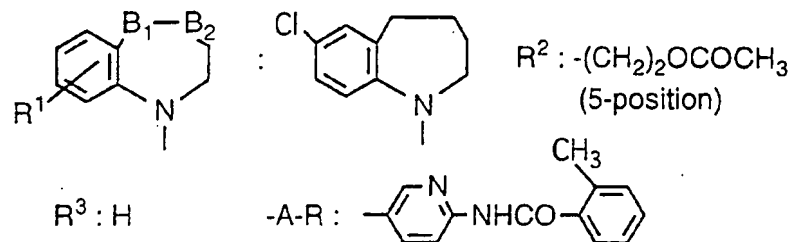
Recrystallization solvent: Dichloromethane-diethyl ether

Melting Point: 168 - 170°C

Form: Free

## Example 124

Structure:



Crystalline form: White powder

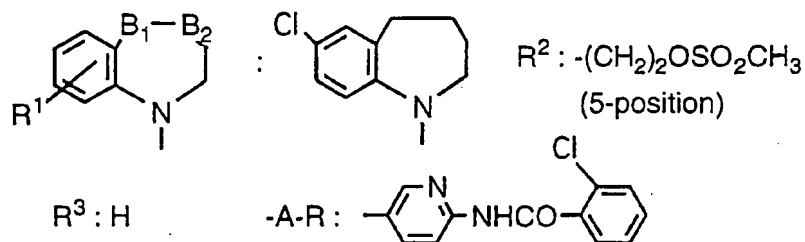
Recrystallization solvent: Dichloromethane-diethyl ether

Melting point: 150 - 153°C

Form: Free

## Example 125

Structure:



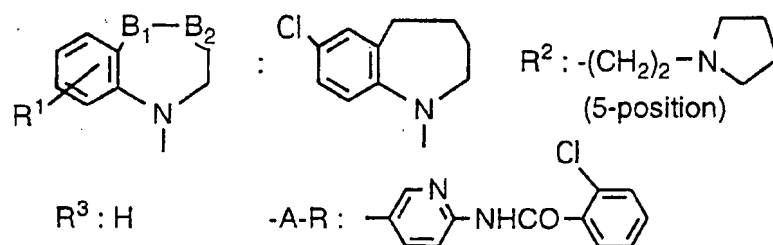
Crystalline form: Colorless amorphous

NMR analysis: 33)

Form: Free

## Example 126

Structure:



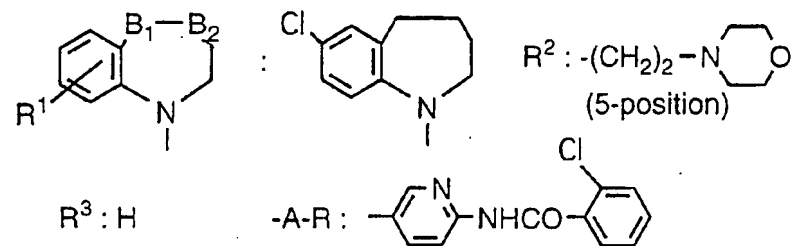
Crystalline form: Colorless amorphous

NMR analysis: 34)

Form: Free

## Example 127

Structure:



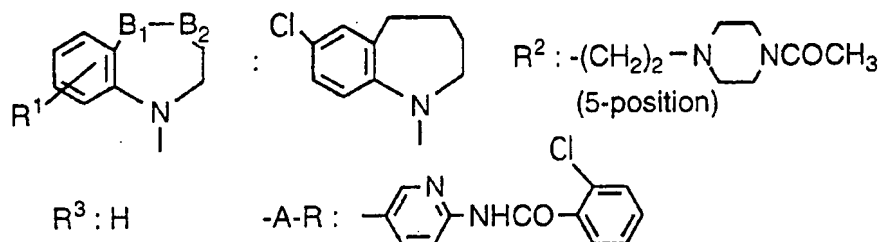
Crystalline form: Yellow amorphous

NMR analysis: 35)

Form: Free

## Example 128

Structure:



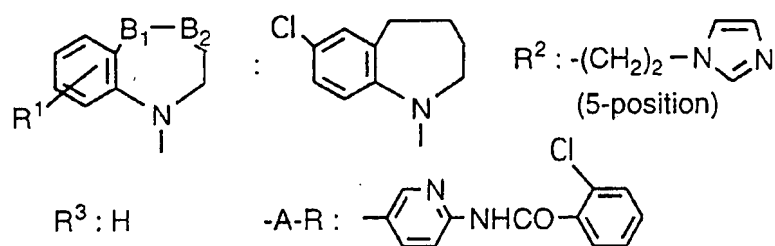
Crystalline form: Yellow amorphous

NMR analysis: 36)

Form: Free

## Example 129

Structure:



Crystalline form: White powder

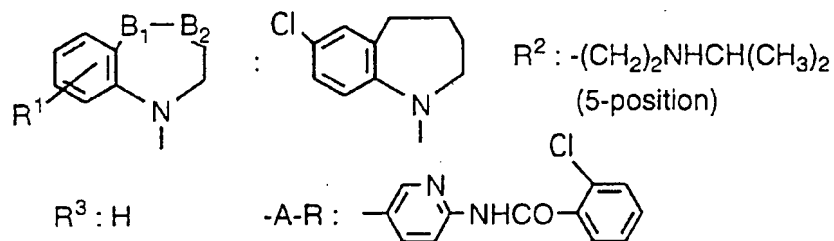
Recrystallization solvent: Dichloromethane-diethyl ether

Melting Point: 201 - 204°C

Form: Free

## Example 130

Structure:



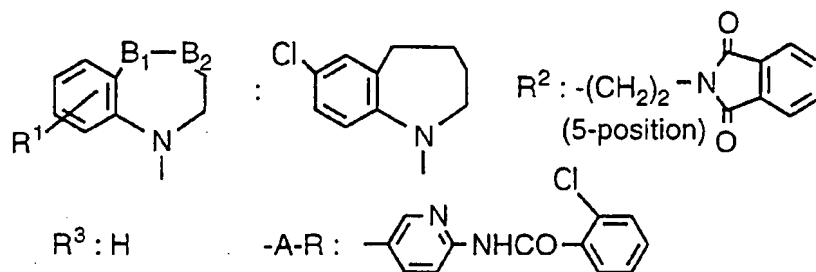
Crystalline form: Colorless amorphous

NMR analysis: 37)

Form: Free

## Example 131

Structure:



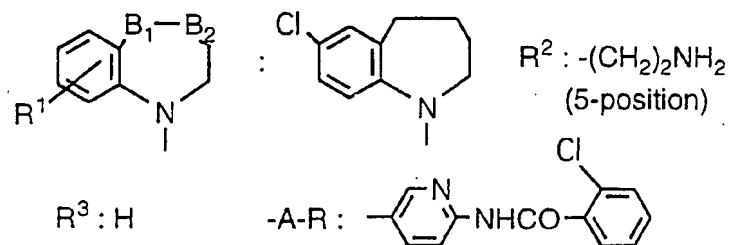
Crystalline form: Colorless amorphous

NMR analysis: 38)

Form: Free

## Example 132

Structure:



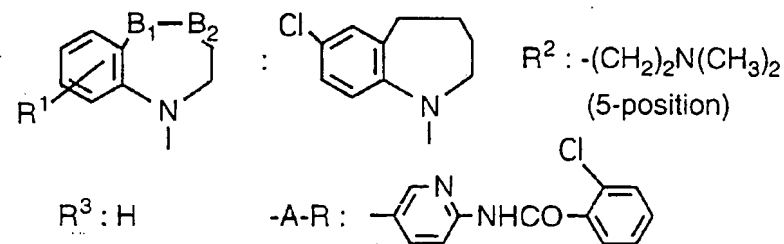
Crystalline form: Colorless amorphous

NMR analysis: 39)

Form: Free

## Example 133

Structure:



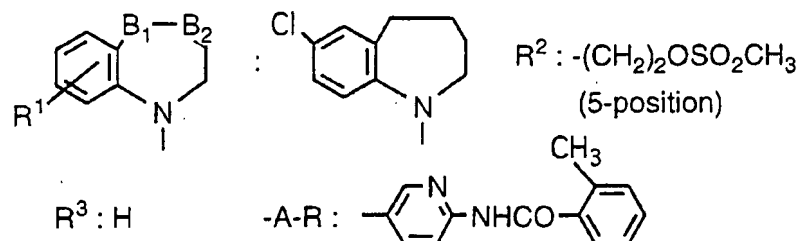
Crystalline form: Colorless amorphous

NMR analysis: 40)

Form: Free

## Example 134

Structure:



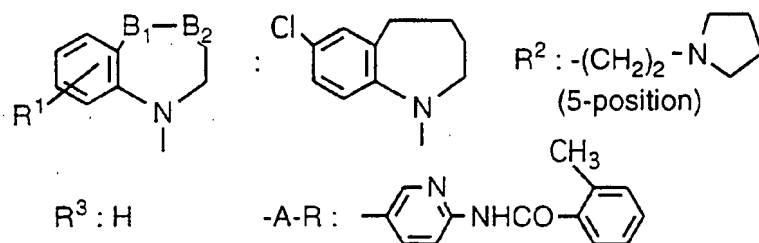
Crystalline form: Colorless amorphous

NMR analysis: 41)

Form: Free

## Example 135

Structure:



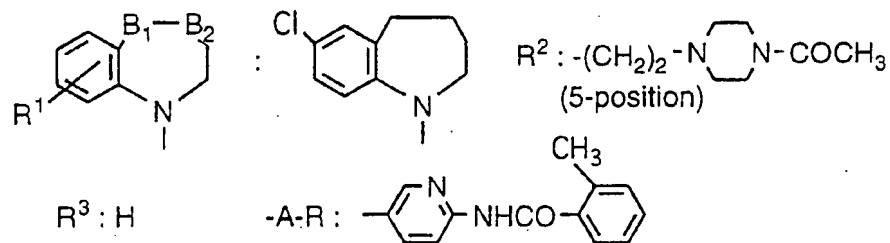
Crystalline form: Yellow amorphous

NMR analysis: 42)

Form: Free

## Example 136

Structure:



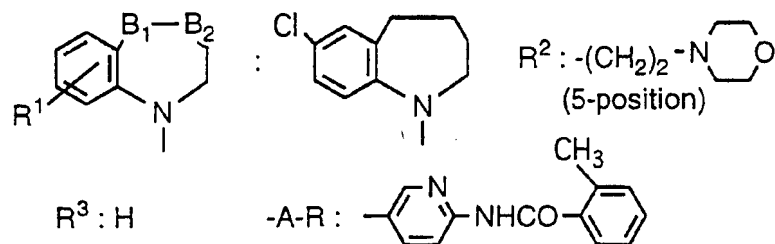
Crystalline form: Yellow amorphous

NMR analysis: 43)

Form: Free

## Example 137

Structure:



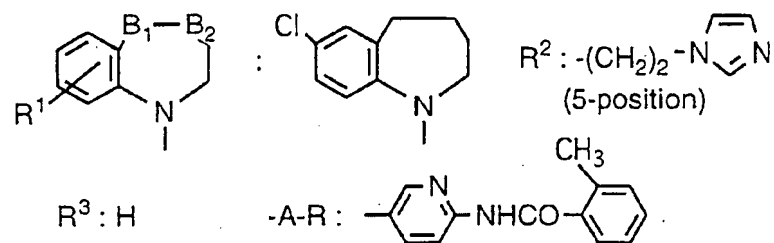
Crystalline form: Yellow amorphous

NMR analysis: 44)

Form: Free

## Example 138

Structure:



Crystalline form: White powder

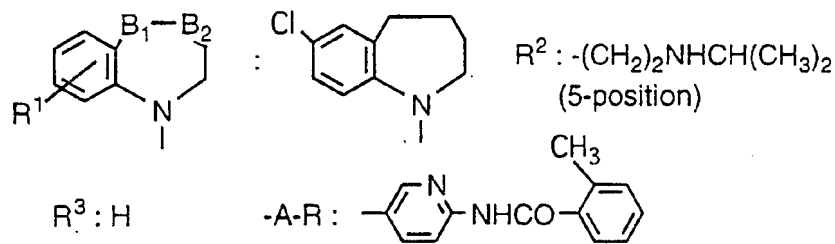
Recrystallization solvent: Dichloromethane-diethyl ether

Melting Point: 192 - 195°C

Form: Free

## Example 139

Structure:



Crystalline form: Yellow amorphous

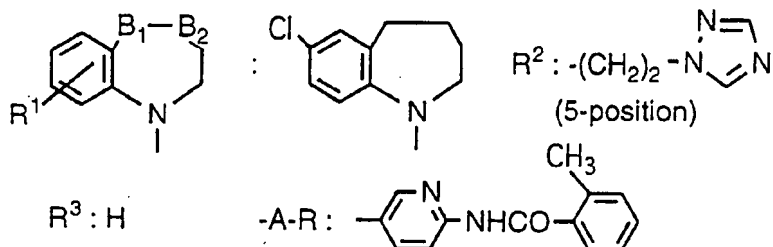
NMR analysis: 45)

Form: Free



## Example 140

Structure:



Crystalline form: White powder

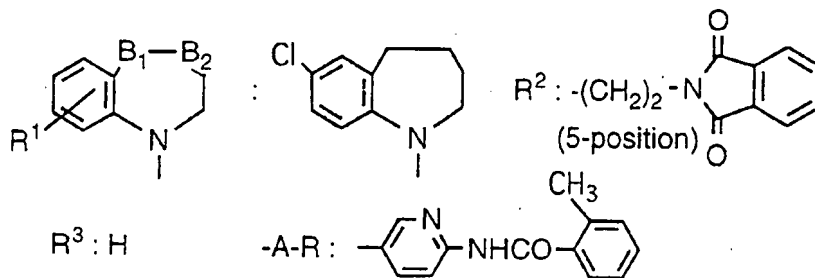
Recrystallization solvent: Dichloromethane-diethyl ether

Melting point: 149 - 152°C

Form: Free

## Example 141

Structure:



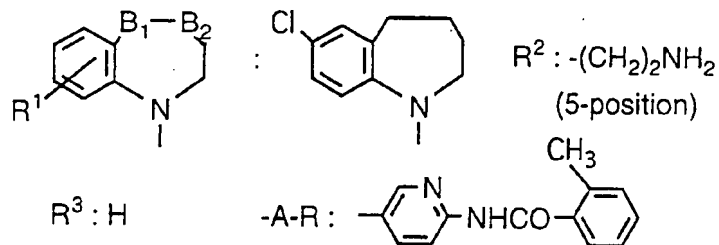
Crystalline form: Colorless amorphous

NMR analysis: 46)

Form: Free

## Example 142

Structure:



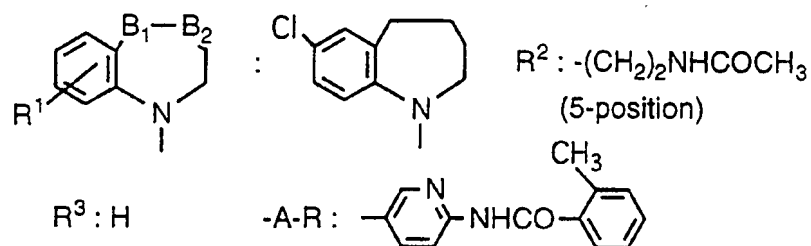
Crystalline form: Colorless amorphous

NMR analysis: 47)

Form: Free

## Example 143

Structure:



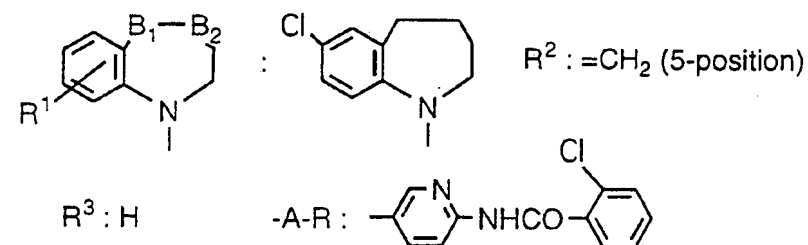
Crystalline form: White powder

NMR analysis: 48)

Form: Free

## Example 144

Structure:



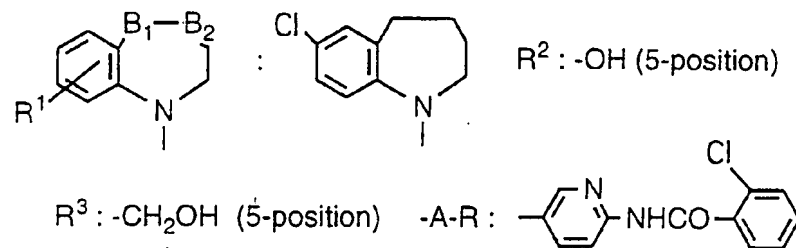
Crystalline form: Colorless amorphous

NMR analysis: 49)

Form: Free

## Example 145

Structure:



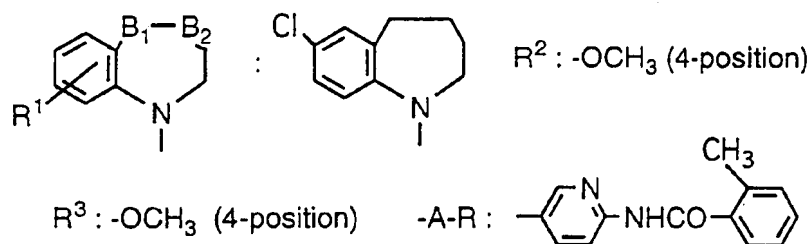
Crystalline form: Colorless amorphous

NMR analysis: 50)

Form: Free

## Example 146

Structure:



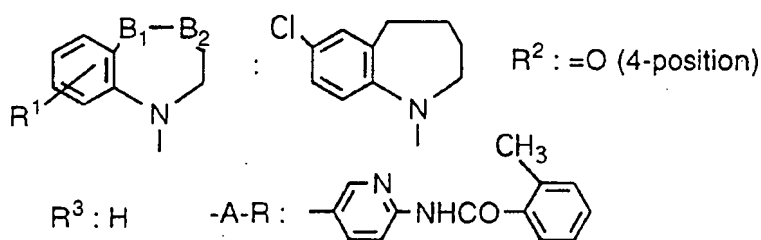
Crystalline form: Colorless amorphous

NMR analysis: 51)

Form: Free

## Example 147

Structure:



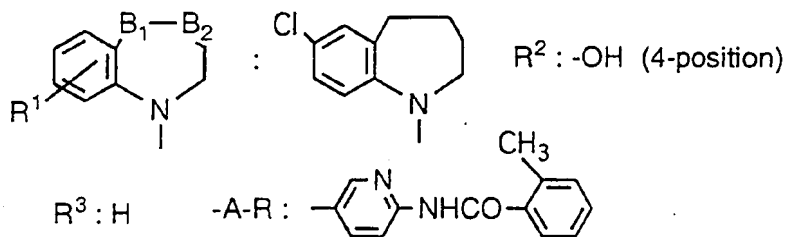
Crystalline form: Colorless amorphous

NMR analysis: 52)

Form: Free

## Example 148

Structure:



Crystalline form: Colorless amorphous

NMR analysis: 53)

Form: Free

Table 2

- 1)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.60 - 2.60 (4H, m), 2.46 (3H, s), 2.70 - 2.95 (1H, m), 3.73 (1H, s), 4.65 - 5.65 (2H, m), 6.57 (1H, d,  $J=8.1$  Hz), 7.00 (1H, d,  $J=6.5$  Hz), 7.15 - 8.40 (8H, m), 8.70 - 8.90 (1H, m)
- 5      2)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.60 - 2.45 (4H, m), 2.41 (3H, s), 2.70 - 3.30 (2H, m), 4.65 - 5.70 (2H, m), 6.60 (1H, d,  $J=8.4$  Hz), 7.01 (1H, dd,  $J=2, 8.1$  Hz), 7.20 - 7.50 (2H, m), 7.50 - 7.90 (4H, m), 8.05 - 8.40 (2H, m), 8.72 (1H, s)
- 10      3)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.60 - 2.45 (4H, m), 2.41 (3H, s), 2.70 - 2.90 (1H, m), 3.20 - 3.60 (1H, m), 4.65 - 5.70 (2H, m), 6.59 (1H, d,  $J=8.2$  Hz), 7.00 (1H, dd,  $J=2, 8.1$  Hz), 7.15 - 7.30 (2H, m), 7.50 - 7.85 (4H, m), 8.05 - 8.40 (2H, m), 8.77 (1H, s)
- 4)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.60 - 2.90 (6H, m), 4.06 (3H, s), 4.75 - 5.20 (2H, m), 6.61 (1H, d,  $J=8$  Hz), 6.95 - 7.25 (3H, m), 7.45 - 7.85 (3H, m), 8.10 - 8.50 (3H, m), 10.39 (1H, s)
- 15      5)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.50 - 2.50 (4H, m), 2.60 - 2.90 (1H, m), 3.40 - 3.70 (1H, m), 4.60 - 5.20 (2H, m), 6.56 (1H, d,  $J=8.2$  Hz), 7.01 (1H, dd,  $J=2.1, 8.3$  Hz), 7.20 - 7.90 (6H, m), 7.90 - 8.20 (2H, m), 9.29 (1H, s)
- 20      6)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.55 - 2.60 (4H, m), 2.65 - 2.95 (1H, m), 3.20 - 3.60 (1H, m), 4.70 - 5.25 (2H, m), 6.58 (1H, d,  $J=8.2$  Hz), 7.01 (1H, d,  $J=8.1$  Hz), 7.10 - 7.90 (6H, m), 7.90 - 8.40 (2H, m), 9.04 (1H, s)
- 7)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.60 - 2.50 (4H, m), 2.70 - 2.90 (1H, m), 3.40 - 3.80 (1H, m), 4.70 - 5.20 (2H, m), 6.59 (1H, d,  $J=8.3$  Hz), 7.00 (1H, dd,  $J=2.3, 8.3$  Hz), 7.10 - 7.15 (1H, m), 7.55 - 7.60 (2H, m), 7.60 - 7.85 (2H, m), 8.00 - 8.40 (2H, m), 8.81 (1H, s)
- 25      8)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.20 - 2.40 (15H, m), 2.70 - 3.00 (1H, m), 3.20 - 3.40 (1H, m), 4.70 - 5.20 (2H, m), 6.57 (1H, d,  $J=8.3$  Hz), 7.00 (1H, d,  $J=8.4$  Hz), 7.47 (1H, d,  $J=8.8$  Hz), 7.71 (1H, s), 8.00 - 8.35 (3H, m)
- 9)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.60 - 2.40 (4H, m), 2.30 (3H, s), 2.65 - 3.10 (2H,

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m), 3.74 (2H, s), 4.70 - 5.15 (2H, m), 6.54 (1H, d, J=8.3 Hz), 6.97 (1H, dd, J=2.1, 8.3 Hz), 7.20 - 7.30 (4H, m), 7.45 - 7.85 (2H, m), 7.88 (1H, s), 7.90 - 8.30 (2H, m)

5 10)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.50 - 2.60 (3H, m), 2.45 (3H, s), 2.60 - 2.95 (1H, m), 3.60 - 4.25 (4H, m), 4.70 - 5.10 (1H, m), 6.54 (1H, d, J=8.3 Hz), 6.99 (1H, dd, J=2.3, 8.3 Hz), 7.10 - 7.70 (5H, m), 7.82 (1H, d, J=2.3 Hz), 8.10 - 8.30 (2H, m), 8.83 (1H, s)

10 11)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.60 - 2.60 (8H, m), 2.29, 2.32 (3H, s), 2.50 (3H, s), 2.70 - 3.05 (1H, m), 3.40 - 3.80 (4H, m), 4.10 - 4.50 (2H, m), 4.55 - 5.20 (2H, m), 6.60 - 6.75 (1H, m), 7.00 - 7.15 (1H, m), 7.15 - 7.85 (6H, m), 8.10 - 8.40 (3H, m)

12)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.50 - 2.60 (4H, m), 2.51 (3H, s), 2.70 - 3.05 (1H, m), 3.50 - 4.05 (4H, m), 4.50 - 5.15 (2H, m), 6.60 - 6.75 (1H, m), 7.00 - 7.15 (1H, m), 7.20 - 7.85 (6H, m), 8.10 - 8.40 (3H, m)

15 13)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.50 - 3.00 (13H, m), 2.50 (3H, s), 3.40 - 3.85 (2H, m), 4.45 - 5.15 (2H, m), 6.60 (1H, d, J=8.1 Hz), 7.00 - 7.10 (1H, m), 7.20 - 7.90 (6H, m), 8.05 - 8.60 (3H, m)

20 14)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.60 - 2.70 (6H, m), 2.50 (3H, s), 2.70 - 3.00 (1H, m), 3.00 - 3.20 (1H, m), 3.40 - 3.80 (4H, m), 4.50 - 5.10 (2H, m), 5.95 - 6.15 (1H, m), 6.65 - 6.80 (1H, m), 7.00 - 7.20 (1H, m), 7.20 - 7.80 (6H, m), 8.05 - 8.50 (3H, m)

15)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.20 - 3.95 (16H, m), 2.34 (3H, s), 2.50 (3H, s), 4.40 - 5.15 (1H, m), 6.61 (1H, d, J=8.3 Hz), 6.97 (1H, dd, J=2.1, 8.3 Hz), 7.03 (1H, s), 7.20 - 7.40 (3H, m), 7.48 (1H, d, J=7.6 Hz), 7.83 (1H, dd, J=2.1, 8.8 Hz), 8.20 (1H, d, J=8.8 Hz), 8.31 (1H, s), 8.38 (1H, d, J=2.1 Hz)

25 16)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.43 (3H, s), 2.49 (3H, s), 3.04 (3H, s), 3.70 (1H, d, J=14 Hz), 4.02 (1H, d, J=14 Hz), 4.85 - 5.10 (1H, m), 6.61 (1H, d, J=8.3 Hz), 7.03 (1H, dd, J=2.4, 8.3 Hz), 7.20 - 7.60 (6H, m), 8.01 (1H, d, J=1.7 Hz), 8.12 (1H, d, J=8.7 Hz), 8.67 (1H, s)

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- 17)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.75 - 2.20 (2H, m), 2.80 - 3.30 (2H, m), 2.96 (3H, s), 3.40 - 3.65 (1H, m), 4.45 - 4.70 (1H, m), 6.52 (1H, d,  $J=8.2$  Hz), 6.62 (1H, dd,  $J=1.8, 8.2$  Hz), 6.90 (1H, d,  $J=1.9$  Hz), 7.30 - 7.55 (4H, m), 7.66 (1H, d,  $J=7.1$  Hz), 7.95 (1H, d,  $J=1.6$  Hz), 8.16 (1H, d,  $J=8.6$  Hz), 9.14 (1H, s)
- 5 18)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.20 - 2.60 (10H, m), 2.44 (3H, s), 3.15 - 3.65 (2H, m), 4.00 - 5.00 (1H, m), 6.50 (2H, s), 6.90 - 7.50 (6H, m), 7.67 (1H, s), 8.73 (1H, s)
- 10 19)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.85 - 2.20 (2H, m), 2.30 - 3.30 (3H, m), 2.50 (3H, s), 4.75 - 5.15 (1H, m), 5.20 - 5.35 (2H, m), 6.61 (1H, d,  $J=8.3$  Hz), 7.01 (1H, dd,  $J=2.5, 8.4$  Hz), 7.20 - 7.60 (6H, m), 8.06 (1H, d,  $J=2$  Hz), 8.19 (1H, d,  $J=8.7$  Hz), 8.34 (1H, s)
- 15 20)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.00 - 2.40 (2H, m), 2.30 (3H, s), 2.85 (2H, t,  $J=6.2$  Hz), 3.74 (2H, s), 3.40 - 4.60 (2H, m), 6.66 (1H, d,  $J=8.4$  Hz), 7.15 - 7.30 (5H, m), 7.52 (1H, dd,  $J=2.4, 8.6$  Hz), 7.74 (1H, s), 7.82 (1H, d,  $J=2.5$  Hz), 8.05 - 8.15 (2H, m)
- 20 21)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.60 - 2.60 (4H, m), 2.51 (3H, s), 3.70 - 3.80 (3H, m), 4.10 - 4.50 (2H, m), 4.55 - 5.20 (2H, m), 6.60 - 6.70 (1H, m), 7.00 - 7.15 (1H, m), 7.20 - 7.90 (6H, m), 8.10 - 8.45 (3H, m)
- 20 22)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.50 - 2.60 (4H, m), 2.50 (3H, s), 2.70 - 3.20 (1H, m), 2.93, 3.13 (3H, s), 3.70 - 4.05 (2H, m), 4.20 - 5.20 (4H, m), 6.64 (1H, d,  $J=8.1$  Hz), 7.00 - 7.10 (1H, m), 7.20 - 7.85 (6H, m), 8.05 - 8.40 (3H, m)
- 25 23)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.45 - 2.55 (4H, m), 2.51 (3H, s), 2.60 - 2.95 (1H, m), 3.70 - 4.20 (2H, m), 4.50 - 5.15 (2H, m), 6.58 (1H, d,  $J=8.2$  Hz), 6.99 (1H, d,  $J=8.5$  Hz), 7.20 - 8.50 (15H, m)
- 25 24)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.50 - 2.60 (4H, m), 2.50 (3H, s), 2.65 - 3.20 (3H, m), 3.40 - 3.80 (2H, m), 4.45 - 5.15 (2H, m), 6.62 (1H, d,  $J=8.1$  Hz), 7.04 (1H, d,  $J=8.1$  Hz), 7.15 - 7.85 (6H, m), 8.10 - 8.50 (3H, m)
- 25 25)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.60 - 2.50 (3H, m), 2.65 - 2.90 (1H, m), 3.20 -

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3.35 (1H, m), 3.81 (3H, s), 4.70 - 5.15 (2H, m), 6.57 (1H, d, J=8.3 Hz), 7.01 (1H, d, J=8.2 Hz), 7.20 - 8.25 (8H, m), 8.85 - 9.15 (1H, m)

26) <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.40 - 1.70 (1H, m), 1.85 - 2.20 (3H, m), 2.70 - 3.15 (3H, m), 3.06 (3H, s), 4.45 - 4.55 (2H, m), 4.60 - 4.70 (2H, m), 4.95 - 5.15 (1H, m), 6.62 (1H, d, J=8.2 Hz), 6.97 (2H, t, J=8.2 Hz), 7.17 (1H, t, J=7.2 Hz), 7.28 (1H, s), 7.45 - 7.60 (2H, m), 8.09 (1H, s), 8.15 - 8.30 (2H, m), 10.23 (1H, s)

27) <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.18 (6H, d, J=6.4 Hz), 1.30 - 1.60 (1H, m), 1.70 - 2.15 (3H, m), 2.10 - 3.20 (3H, m), 3.20 - 3.55 (3H, m), 4.40 - 4.55 (2H, m), 4.75 - 4.95 (1H, m), 6.89 (1H, d, J=8.4 Hz), 7.05 - 7.25 (3H, m), 7.45 - 7.80 (4H, m), 8.01 (1H, s), 8.11 (1H, d, J=8.6 Hz), 9.27 (2H, brs), 10.71 (1H, s)

28) <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.30 - 1.65 (1H, m), 1.90 - 2.20 (3H, m), 2.60 - 3.10 (3H, m), 4.10 - 4.30 (2H, m), 4.40 - 4.60 (2H, m), 4.90 - 5.10 (1H, m), 6.60 (1H, d, J=8 Hz), 6.90 - 7.00 (1H, m), 7.00 - 7.15 (2H, m), 7.25 - 7.30 (1H, m), 7.40 - 7.55 (2H, m), 7.60 - 7.85 (4H, m), 7.97 (1H, s), 8.10 - 8.20 (2H, m), 10.05 (1H, s)

29) <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.35 - 2.20 (4H, m), 2.60 - 3.40 (5H, m), 4.15 - 4.30 (2H, m), 4.90 - 5.10 (1H, m), 6.61 (1H, d, J=8.2 Hz), 6.90 - 7.30 (4H, m), 7.40 - 7.55 (2H, m), 8.15 - 8.25 (3H, m), 10.81 (1H, s)

30) <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.30 - 1.60 (1H, m), 1.80 - 2.15 (3H, m), 2.79 (6H, s), 2.60 - 3.20 (3H, m), 3.55 (2H, s), 4.53 (2H, s), 4.75 - 4.90 (1H, m), 5.60 (1H, brs), 6.87 (1H, d, J=8.4 Hz), 7.05 - 7.25 (3H, m), 7.45 - 7.75 (4H, m), 8.05 - 8.15 (2H, m), 10.69 (1H, s), 10.90 (1H, brs)

31) <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.30 - 2.15 (4H, m), 2.49 (3H, s), 2.62 (6H, s), 2.30 - 3.90 (8H, m), 4.35 - 4.55, 5.10 - 5.30 (1H, m), 6.60 (1H, d, J=8.3 Hz), 6.90 - 7.05 (1H, m), 7.20 - 7.80 (7H, m), 8.15 (1H, d, J=8.5 Hz), 8.30 - 8.40 (2H, m)

32) <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.30 - 2.10 (4H, m), 1.49 (9H, s), 2.60 - 3.95 (12H, m), 4.40 - 4.60, 5.05 - 5.20 (1H, m), 6.58 (1H, d, J=8.2 Hz), 6.90 - 7.05 (2H, m), 7.30 - 7.50 (3H, m), 7.60 - 7.90 (2H, m), 8.00 - 8.25 (1H, m), 8.35 (1H,

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d, J=2 Hz), 8.75 (1H, s)

33)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.30 - 2.50 (6H, m), 2.55 - 3.45 (2H, m), 3.04 (3H, s), 4.20 - 4.60, 5.10 - 5.25 (3H, m), 6.64 (1H, d, J=8.3 Hz), 7.03 (1H, d, J=8.2 Hz), 7.15 - 7.50 (5H, m), 7.56 (1H, d, J=8.6 Hz), 7.72 (1H, d, J=6.2 Hz), 8.09 (1H, s), 8.21 (1H, d, J=8.7 Hz), 8.74 (1H, s)

34)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.30 - 2.80 (14H, m), 3.05 - 3.40 (2H, m), 4.25 - 4.45, 5.05 - 5.25 (1H, m), 6.60 (1H, d, J=8.2 Hz), 6.90 - 7.05 (1H, m), 7.25 - 7.60 (5H, m), 7.72 (1H, d, J=6.4 Hz), 8.17 (1H, d, J=8.1 Hz), 8.70 (1H, s)

35)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.30 - 2.80 (12H, m), 3.05 - 3.40 (2H, m), 3.60 - 3.90 (4H, m), 4.30 - 4.60, 5.05 - 5.25 (1H, m), 6.61 (1H, d, J=8.2 Hz), 6.90 - 7.10 (1H, m), 7.20 - 7.70 (5H, m), 7.72 (1H, d, J=6.2 Hz), 8.10 - 8.30 (2H, m), 8.69 (1H, s)

36)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.25 - 2.30 (6H, m), 2.07 (3H, s), 2.30 - 2.80 (6H, m), 3.00 - 3.70 (6H, m), 4.30 - 4.50, 5.10 - 5.25 (1H, m), 6.55 - 6.64 (1H, m), 6.90 - 7.05 (1H, m), 7.20 - 7.30 (1H, m), 7.40 - 7.50 (3H, m), 7.55 - 7.65 (1H, m), 7.73 (1H, d, J=6.3 Hz), 8.10 - 8.25 (2H, m), 8.68 (1H, s)

37)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.04 - 1.12 (6H, m), 1.20 - 2.30 (6H, m), 2.50 - 3.00 (3H, m), 3.00 - 3.40 (2H, m), 4.30 - 4.50, 5.10 - 5.25 (1H, m), 6.50 - 6.65 (1H, m), 6.90 - 7.15 (1H, m), 7.25 - 7.65 (5H, m), 7.73 (1H, d, J=7.2 Hz), 8.17 (1H, d, J=8.9 Hz), 8.70 (1H, brs)

38)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.25 - 2.50 (6H, m), 2.60 - 3.40 (2H, m), 3.70 - 4.00 (2H, m), 4.30 - 4.50, 5.10 - 5.30 (1H, m), 6.62 (1H, d, J=8.5 Hz), 6.90 - 7.15 (1H, m), 7.25 - 7.60 (5H, m), 7.65 - 7.90 (5H, m), 8.00 - 8.30 (2H, m), 8.72 (1H, s)

39)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.20 - 2.30 (6H, m), 2.60 - 3.40 (4H, m), 4.25 - 4.45, 5.05 - 5.25 (1H, m), 6.56 - 6.65 (1H, m), 6.90 - 7.05 (1H, m), 7.20 - 7.60 (5H, m), 7.69 (1H, d, J=6.4 Hz), 8.05 - 8.25 (2H, m), 9.02 (1H, brs)

40)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.20 - 2.80 (8H, m), 2.22, 2.26 (6H, s), 3.05 -



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3.40 (2H, m), 4.25 - 4.44, 5.10 - 5.20 (1H, m), 6.50 - 6.65 (1H, m), 6.90 - 7.05 (1H, m), 7.20 - 7.30 (1H, m), 7.30 - 7.60 (4H, m), 7.71 (1H, d, J=6.3 Hz), 8.15 - 8.20 (2H, m), 8.73 (1H, s)

41)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.20 - 2.80 (6H, m), 2.50 (3H, s), 3.03 (3H, s),  
5 3.10 - 3.50 (2H, m), 4.20 - 4.55, 5.10 - 5.30 (3H, m), 6.65 (1H, d, J=8.4 Hz), 7.03 (1H, d, J=8.4 Hz), 7.20 - 7.65 (6H, m), 8.09 (1H, s), 8.20 - 8.25 (2H, m)

42)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.20 - 2.30 (10H, m), 2.50 (3H, s), 2.30 - 2.80 (6H, m), 3.10 - 3.40 (2H, m), 4.20 - 4.45, 5.05 - 5.25 (1H, m), 6.50 - 6.65 (1H, m), 6.90 - 7.05 (1H, ), 7.20 - 7.60 (6H, m), 8.10 - 8.20 (2H, m), 8.35 (1H, s)

43)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.20 - 2.30 (6H, m), 2.07 (3H, s), 2.50 (3H, s),  
10 2.30 - 2.80 (6H, m), 3.00 - 3.70 (6H, m), 4.25 - 4.45, 5.05 - 5.25 (1H, m), 6.55 - 6.65 (1H, m), 6.95 - 7.05 (1H, m), 7.20 - 7.65 (6H, m), 8.05 - 8.30 (3H, m)

44)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.20 - 2.70 (12H, m), 2.50 (3H, s), 3.00 - 3.40 (2H, m), 3.65 - 3.75 (4H, m), 4.30 - 4.50, 5.10 - 5.30 (1H, m), 6.55 - 6.65 (1H, m),  
15 6.95 - 7.05 (1H, m), 7.25 - 7.60 (6H, m), 8.11 - 8.30 (3H, m)

45)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 0.95 - 1.05 (6H, m), 1.10 - 2.90 (9H, m), 2.42 (3H, s), 2.90 - 3.30 (2H, m), 4.20 - 4.40, 5.00 - 5.20 (1H, m), 6.53 (1H, d, J=8.1 Hz), 6.85 - 7.00 (1H, m), 7.10 - 7.45 (6H, m), 8.00 - 8.15 (2H, m), 8.37 (1H, s)

46)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.20 - 2.70 (6H, m), 2.50 (3H, s), 2.80 - 3.40 (2H, m), 3.70 - 3.95 (2H, m), 4.30 - 4.50, 5.10 - 5.30 (1H, m), 6.63 (1H, d, J=8.6 Hz),  
20 7.00 - 7.05 (1H, m), 7.20 - 7.60 (5H, m), 7.65 - 7.90 (5H, m), 8.00 - 8.35 (3H, m)

47)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.20 - 2.30 (6H, m), 2.50 (3H, s), 2.55 - 3.40 (4H, m), 4.25 - 4.45, 5.10 - 5.25 (1H, m), 6.50 - 6.65 (1H, m), 6.95 - 7.05 (1H, m), 7.20 - 7.60 (6H, m), 8.05 - 8.25 (2H, m), 8.47 (1H, s)

48)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.20 - 2.30 (6H, m), 1.99 (3H, s), 2.50 (3H, s),  
25 2.80 - 3.60 (4H, m), 4.30 - 4.50, 5.05 - 5.25 (1H, m), 5.45 - 5.80 (1H, m), 6.55 - 6.65 (1H, m), 6.95 - 7.05 (1H, m), 7.20 - 7.60 (6H, m), 8.00 - 8.30 (3H, m)

49)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.80 - 2.25 (2H, m), 2.30 - 3.20 (3H, m), 4.70 -

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5.20 (1H, m), 5.26 (1H, s), 5.33 (1H, s), 6.61 (1H, d, J=8.4 Hz), 7.01 (1H, dd, J=1.9, 8.4 Hz), 7.30 - 7.60 (5H, m), 7.71 (1H, dd, J=1.7, 6.3 Hz), 8.06 (1H, d, J=1.7 Hz), 8.18 (1H, d, J=8.7 Hz), 8.75 (1H, s)

50) <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.50 - 2.25 (4H, m), 2.70 - 3.00 (1H, m), 3.40 - 4.20 (4H, m), 4.70 - 5.10 (1H, m), 6.54 (1H, d, J=8.3 Hz), 6.99 (1H, dd, J=2.4, 8.3 Hz), 7.25 - 7.40 (3H, m), 7.55 - 7.65 (2H, m), 7.84 (1H, d, J=2.4 Hz), 8.10 - 8.20 (2H, m), 9.07 (1H, s)

51) <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 2.00 - 2.15 (2H, m), 2.49 (3H, s), 3.13 (2H, s), 3.20 (3H, s), 3.31 (3H, s), 3.10 - 3.35 (1H, m), 4.70 - 4.85 (1H, m), 6.58 (1H, d, J=8.4 Hz), 7.00 (1H, dd, J=2.3, 8.3 Hz), 7.20 - 7.55 (6H, m), 7.95 (1H, d, J=1.8 Hz), 8.20 (1H, d, J=8.7 Hz), 8.55 (1H, s)

52) <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 2.50 (3H, s), 2.65 - 3.00 (2H, m), 3.40 - 3.70 (2H, m), 4.00 - 4.30 (1H, m), 4.65 - 5.00 (1H, m), 6.73 (1H, d, J=8.4 Hz), 7.11 (1H, dd, J=2.4, 8.4 Hz), 7.20 - 7.65 (6H, m), 8.07 (1H, d, J=1.7 Hz), 8.24 (1H, d, J=8.7 Hz), 8.50 (1H, s)

53) <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.80 - 2.30 (2H, m), 2.49 (3H, s), 2.75 - 3.40 (3H, m), 3.75 - 4.00, 4.30 - 4.45 (1H, m), 4.70 - 5.10 (1H, m), 6.55 - 6.65 (1H, m), 7.01 (1H, d, J=8.3 Hz), 7.20 - 7.60 (6H, m), 8.01 (1H, s), 8.20 (1H, d, J=8.6 Hz), 8.50 (1H, s)

54) <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.55 - 2.50 (4H, m), 2.51 (3H, s), 2.65 - 3.00 (1H, m), 4.00 - 4.25 (2H, m), 4.45 - 4.80 (2H, m), 5.00 - 5.45 (2H, m), 5.75 - 6.15 (1H, m), 6.61 (1H, d, J=8.1 Hz), 7.03 (1H, d, J=8.2 Hz), 7.20 - 7.80 (6H, m), 8.05 - 8.40 (3H, m)

55) <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 0.35 - 0.65 (4H, m), 1.35 - 2.40 (6H, m), 2.50 (3H, s), 2.60 - 3.30 (1H, m), 3.90 - 5.20 (2H, m), 6.62 (1H, d, J=8.2 Hz), 6.95 - 7.10 (1H, m), 7.20 - 7.85 (6H, m), 8.15 - 8.40 (3H, m)

56) <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.25 - 2.20 (4H, m), 2.40 - 3.00 (5H, m), 3.10 - 3.35 (1H, m), 3.50 - 3.90 (1H, m), 4.40 - 4.55, 5.00 - 5.15 (1H, m), 5.90 - 6.10

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(1H, m), 6.59 (1H, d, J=8.3 Hz), 6.98 (1H, d, J=8.3 Hz), 7.12 (1H, d, J=2.1 Hz), 7.30 - 7.60 (3H, m), 7.60 - 7.75 (2H, m), 8.10 - 8.30 (2H, m), 8.94 (1H, s)

#### Example 149

To a suspension of 7-chloro-5-hydroxy-1-[6-(2-methoxycarbonyl-  
5 benzoylamino)nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (0.3 g) in  
methanol (4 ml) is added 5 % aqueous sodium hydroxide solution (1.5 ml), and  
the mixture is stirred at room temperature for one hour. To the reaction solution  
are added water and diluted aqueous hydrochloric acid solution in order to  
make the mixture weak acidic. The mixture is extracted with dichloromethane,  
10 and the extract is washed with water, dried over magnesium sulfate and  
evaporated under reduced pressure to remove the solvent. The residue is  
recrystallized from dichloromethane-methanol to give 7-chloro-5-hydroxy-1-[6-  
(2-carboxybenzoylamino)nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (150  
mg) as white powder.

15 M.p. 153 - 155°C

Using the suitable starting compounds, there are obtained the  
compounds of Examples 83, 85 and 86 in the same manner as in Example  
149.

#### Example 150

20 To a solution of 7-chloro-1-[6-[2-(3-ethoxycarbonylpropoxy)benzoyl-  
amino]nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (2.5 g) in ethylene glycol  
dimethyl ether (70 ml) is added sodium trimethoxyborohydride (3.78 g), and the  
mixture is refluxed for 3 hours. The reaction solution is gradually poured into  
diluted hydrochloric acid, and the mixture is extracted with ethyl acetate. The  
25 extract is washed with water, dried over magnesium sulfate, and evaporated  
under reduced pressure to remove the solvent. The residue is purified by silica  
gel column chromatography, and recrystallized from dichloromethane-diethyl  
ether to give 7-chloro-1-[6-[2-(4-hydroxybutoxy)benzoylamino]nicotinoyl]-  
2,3,4,5-tetrahydro-1H-benzazepine (1.12 g) as white powder.

30 M.p. 157 - 158.5°C

Using the suitable starting compounds, there is obtained the

compound of Example 83 in the same manner as in Example 150.

Example 151

To a solution of 7-chloro-1-[6-(2-carboxymethoxybenzoylamino)-  
nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (0.4 g) in dichloromethane (10  
5 ml) is added with stirring N,N-bis(2-oxo-3-oxazolidinyl)phosphinic chloride  
(0.25 g) under ice-cooling, and the mixture is stirred at room temperature for 15  
minutes. Subsequently, to the reaction mixture is added N-methylpiperazine  
(0.11 ml), and thereto is added triethylamine (0.23 ml). The mixture is stirred at  
room temperature overnight, and thereto is added water. The mixture is  
10 extracted with dichloromethane, and the extract is washed successively with  
diluted aqueous sodium hydroxide solution and water, dried over magnesium  
sulfate, and evaporated under reduced pressure to remove the solvent. The  
residue is purified by silica gel column chromatography, and recrystallized from  
dichloromethane-diethyl ether to give 7-chloro-1-[6-[2-(4-methyl-1-piperazinyl)-  
15 carbonylmethoxybenzoylamino]nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine  
(390 mg) as white powder.

M.p. 111 - 114°C

Using the suitable starting compounds, there are obtained the  
compounds of Examples 89 and 97 in the same manner as in Example 151.

20 Example 152

To a solution of 7-chloro-1-[6-[2-(2-hydroxyethoxy)benzoylamino]-  
nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (0.5 g) in pyridine (10 ml) is  
added with stirring methanesulfonyl chloride (0.1 ml) under ice-cooling, and the  
mixture is stirred at room temperature for 2 hours. To the reaction solution is  
25 added water, and the precipitated crystals are collected by filtration, and  
dissolved in dichloromethane. The mixture is washed successively with diluted  
hydrochloric acid and water, dried over magnesium sulfate and evaporated  
under reduced pressure. The residue is crystallized from diethyl ether to give  
7-chloro-1-[6-[2-(2-methanesulfonyloxyethoxy)benzoylamino]nicotinoyl]-  
30 2,3,4,5-tetrahydro-1H-benzazepine (0.59 g) as white powder.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.40 - 1.70 (1H, m), 1.85 - 2.20 (3H, m), 2.70 -

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3.15 (3H, m), 3.06 (3H, s), 4.45 - 4.55 (2H, m), 4.60 - 4.70 (2H, m), 4.95 - 5.15 (1H, m), 6.62 (1H, d, J=8.2 Hz), 6.97 (2H, t, J=8.2 Hz), 7.17 (1H, t, J=7.2 Hz), 7.28 (1H, s), 7.45 - 7.60 (2H, m), 8.09 (1H, s), 8.15 - 8.30 (2H, m), 10.23 (1H, s)

#### Example 153

5 To a solution of 7-chloro-1-{6-[2-(2-methanesulfonyloxyethoxy)-benzoylamino]nicotinoyl}-2,3,4,5-tetrahydro-1H-benzazepine (0.6 g) in dimethylformamide (5 ml) are added sodium iodide (0.22 g), potassium carbonate (0.23 g) and 4-acetylamino piperidine (0.2 g), and the mixture is heated with stirring at 110°C for 2 hours. The mixture is cooled, and thereto is  
10 added water, and the mixture is extracted with dichloromethane. The extract is washed with water, dried over magnesium sulfate, and evaporated under reduced pressure to remove the solvent. The residue is purified by silica gel column chromatography to give 7-chloro-1-{6-[2-(4-acetylamino-1-piperidinyl)-ethoxy]benzoylamino]nicotinoyl}-2,3,4,5-tetrahydro-1H-benzazepine (0.3 g) as  
15 white powder.

M.p. 159 - 162°C

Using the suitable starting compounds, there are obtained the compounds of Examples 91, 93, 95 and 96 in the same manner as in Example  
153.

#### 20 Example 154

To a solution of 7-chloro-1-{6-[2-(2-methanesulfonyloxyethoxy)-benzoylamino]nicotinoyl}-2,3,4,5-tetrahydro-1H-benzazepine (0.75 g) in dimethylformamide (10 ml) is added potassium phthalimide (0.26 g), and the mixture is stirred at 110°C for one hour. The mixture is poured into ice-water,  
25 and extracted with dichloromethane. The extract is washed with water, dried over magnesium sulfate, and evaporated under reduced pressure. The residue is purified by silica gel column chromatography to give 7-chloro-1-[6-(6,7-benzo-1-oxo-4-azepin-5-on-4-yl)nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (0.23 g, Compound A) and 7-chloro-1-{6-[2-(2-phthalimido-ethoxy)benzoylamino]nicotinoyl}-2,3,4,5-tetrahydro-1H-benzazepine (0.25 g,  
30 Compound B), separately.

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## Compound A

White powder

M.p. 176 - 179°C (recrystallized from ethyl acetate)

## Compound B

5

White powder

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.30 - 1.65 (1H, m), 1.90 - 2.20 (3H, m), 2.60 - 3.10 (3H, m), 4.10 - 4.30 (2H, m), 4.40 - 4.60 (2H, m), 4.90 - 5.10 (1H, m), 6.60 (1H, d,  $J=8$  Hz), 6.90 - 7.00 (2H, m), 7.00 - 7.15 (2H, m), 7.25 - 7.30 (1H, m), 7.40 - 7.55 (2H, m), 7.60 - 7.85 (4H, m), 7.97 (1H, s), 8.10 - 8.20 (2H, m), 10.05 (1H, s)

10

Example 155

To a solution of 7-chloro-1-{6-[2-(2-phthalimidoethoxy)benzoyl-amino]nicotinoyl}-2,3,4,5-tetrahydro-1H-benzazepine (0.25 g) in ethanol (5 ml) is added hydrazine monohydrate (0.03 ml), and the mixture is refluxed for one hour, and cooled. To the mixture is added water, and the mixture is made  
15 acidic with diluted hydrochloric acid, and washed with diethyl ether. The aqueous layer is made basic with aqueous sodium hydroxide solution, and extracted with dichloromethane. The extract is washed with water, dried over magnesium sulfate, and evaporated under reduced pressure to remove the solvent. The residue is crystallized from diethyl ether to give 7-chloro-1-{6-[2-  
20 (2-aminoethoxy)benzoylamino]nicotinoyl}-2,3,4,5-tetrahydro-1H-benzazepine (110 mg) as white powder.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.35 - 2.20 (4H, m), 2.60 - 3.40 (5H, m), 4.15 - 4.30 (2H, m), 4.90 - 5.10 (1H, m), 6.61 (1H, d,  $J=8.2$  Hz), 6.90 - 7.30 (4H, m), 7.40 - 7.55 (2H, m), 8.15 - 8.25 (3H, m), 10.81 (1H, s)

25

Example 156

To a solution of 7-chloro-1-{6-[2-(2-aminoethoxy)benzoylamino]-nicotinoyl}-2,3,4,5-tetrahydro-1H-benzazepine (0.11 g) in methanol (3 ml) is added 37 % formalin (0.24 ml), and thereto is added sodium cyanoborohydride (0.044 g), and thereto is added with stirring acetic acid (0.18 ml) at 10°C. The  
30 mixture is stirred at room temperature for one hour, and poured into ice-water,

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and the mixture is made basic with potassium carbonate, and extracted with dichloromethane. The extract is washed with water, dried over magnesium sulfate, and evaporated under reduced pressure to remove the solvent. The residue is purified by silica gel column chromatography, and the resultant is dissolved in ethanol (5 ml), and thereto is added conc. hydrochloric acid, and the mixture is stirred at room temperature for one hour. The mixture is evaporated under reduced pressure to remove the solvent, and crystallized from diethyl ether to give 7-chloro-1-{6-[2-(2-dimethylaminoethoxy)benzoyl-amino]nicotinoyl}-2,3,4,5-tetrahydro-1H-benzazepine dihydrochloride (53 mg) as white powder.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ : 1.30 - 1.60 (1H, m), 1.80 - 2.15 (3H, m), 2.79 (6H, s), 2.60 - 3.20 (3H, m), 3.55 (2H, s), 4.53 (2H, s), 4.75 - 4.90 (1H, m), 5.60 (1H, brs), 6.87 (1H, d, J=8.4 Hz), 7.05 - 7.25 (3H, m), 7.45 - 7.75 (4H, m), 8.05 - 8.15 (2H, m), 10.69 (1H, s), 10.90 (1H, brs)

Using the suitable starting compounds, there is obtained the compound of Example 91 in the same manner as in Example 156.

#### Example 157

To a solution of 7-chloro-5-(4-t-butoxycarbonyl-1-piperaziny)-carbonylmethyl-1-[6-(2-chlorobenzoylamino)nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (1.2 g) in dioxane (20 ml) is added 5 N hydrochloric acid (2 ml), and the mixture is stirred at room temperature overnight. Water is added to the reaction mixture, and the mixture is made basic with aqueous sodium hydroxide solution, and extracted with dichloromethane. The extract is washed with water, dried over magnesium sulfate, and evaporated under reduced pressure to remove the solvent. The residue is purified by silica gel column chromatography, and recrystallized from ethyl acetate-diethyl ether to give 7-chloro-5-(1-piperaziny)carboxymethyl-1-[6-(2-chlorobenzoylamino)nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (0.54 g) as white powder.

M.p. 157 - 160°C

Example 158

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To a solution of 7-chloro-5-methoxycarbonylmethyl-1-[6-(2-chlorobenzoylamino)nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (8 g) in ethylene glycol dimethyl ether (50 ml) is added sodium trimethoxyborohydride (6 g), and the mixture is refluxed for 4 hours. To the mixture is added sodium trimethoxyborohydride (3 g), and the mixture is refluxed for two hours. The reaction solution is gradually poured into diluted aqueous hydrochloric acid solution, and the mixture is extracted with dichloromethane. The extract is washed with water, dried over magnesium sulfate, and evaporated under reduced pressure to remove the solvent. The residue is purified by silica gel column chromatography, and recrystallized from dichloromethane-diethyl ether to give 7-chloro-5-(2-hydroxyethyl)-1-[6-(2-chlorobenzoylamino)nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (3.1 g) as white powder.

M.p. 161 - 163°C

Using the suitable starting compounds, there is obtained the compound of Example 123 in the same manner as in Example 158.

#### Example 159

To a solution of 7-chloro-5-(2-hydroxyethyl)-1-[6-(2-chlorobenzoylamino)nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (0.3 g) in pyridine (6 ml) is added acetic anhydride (0.09 ml), and the mixture is stirred at 80°C for 2 hours. The reaction solution is poured into water, and extracted with ethyl acetate. The extract is washed successively with diluted hydrochloric acid, water and aqueous sodium hydrogen carbonate solution, dried over magnesium sulfate, and evaporated under reduced pressure to remove the solvent. The residue is purified by silica gel column chromatography, and recrystallized from dichloromethane-diethyl ether to give 7-chloro-5-(2-acetyloxyethyl)-1-[6-(2-chlorobenzoylamino)nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (230 mg) as white powder.

M.p. 151 - 153°C

Using the suitable starting compounds, there is obtained the compound of Example 124 in the same manner as in Example 159.

#### Example 160



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To a solution of 7-chloro-5-(2-hydroxyethyl)-1-[6-(2-chlorobenzoylamino)nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (3.7 g) in pyridine (50 ml) is added with stirring methanesulfonyl chloride (0.71 ml) under ice-cooling, and the mixture is stirred at room temperature for 3 hours. Water is added to the reaction solution, and the mixture is extracted with ethyl acetate. The extract is washed successively with diluted hydrochloric acid and water, dried over magnesium sulfate, and evaporated under reduced pressure to remove the solvent. The residue is purified by silica gel column chromatography to give 7-chloro-5-(2-methanesulfonyloxyethyl)-1-[6-(2-chlorobenzoylamino)nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (2.8 g) as colorless amorphous.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  : 1.30 - 2.50 (6H, m), 2.55 - 3.45 (2H, m), 3.04 (3H, s), 4.20 - 4.60, 5.10 - 5.25 (3H, m), 6.64 (1H, d,  $J=8.3$  Hz), 7.03 (1H, d,  $J=8.2$  Hz), 7.15 - 7.50 (5H, m), 7.56 (1H, d,  $J=8.6$  Hz), 7.72 (1H, d,  $J=6.2$  Hz), 8.09 (1H, s), 8.21 (1H, d,  $J=8.7$  Hz), 8.74 (1H, s)

Using the suitable starting compounds, there is obtained the compound of Example 134 in the same manner as Example 160.

#### Example 161

To a solution of 7-chloro-5-(2-methanesulfonyloxyethyl)-1-[6-(2-chlorobenzoylamino)nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (0.4 g) in dimethylformamide (5 ml) are added pyrrolidine (0.09 ml), sodium iodide (0.14 g) and potassium carbonate (0.15 g), and the mixture is stirred at 110°C for 2 hours. Water is added to the reaction solution, and the mixture is extracted with dichloromethane. The extract is washed with water, dried over magnesium sulfate, and evaporated under reduced pressure to remove the solvent. The residue is purified by silica gel column chromatography to give 7-chloro-5-[2-(1-pyrrolidinyl)ethyl]-1-[6-(2-chlorobenzoylamino)nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (98 mg) as colorless amorphous.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  : 1.30 - 2.80 (14H, m), 3.05 - 3.40 (2H, m), 4.25 - 4.45, 5.05 - 5.25 (1H, m), 6.60 (1H, d,  $J=8.2$  Hz), 6.90 - 7.05 (1H, m), 7.25 - 7.60 (5H, m), 7.72 (1H, d,  $J=6.4$  Hz), 8.17 (1H, d,  $J=8.1$  Hz), 8.70 (1H, s)

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Using the suitable starting compounds, there are obtained the compounds of Examples 127 - 133 and 135 - 143 in the same manner as in Example 161.

#### Example 162

5 To a solution of 7-chloro-5-(2-methanesulfonyloxyethyl)-1-[6-(2-chlorobenzoylamino)nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (1.6 g) in dimethylformamide (30 ml) is added potassium phthalimide (0.58 g), and the mixture is stirred at 110°C for 3 hours. The mixture is poured into ice-water, and the mixture is extracted with dichloromethane. The extract is washed with  
10 water, dried over magnesium sulfate, and evaporated under reduced pressure to remove the solvent. The residue is purified by silica gel column chromatography to give 7-chloro-5-(2-phthalimidoethyl)-1-[6-(2-chlorobenzoylamino)nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (1.8 g) as colorless amorphous.

15 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ : 1.25 - 2.50 (6H, m), 2.60 - 3.40 (2H, m), 3.70 - 4.00 (2H, m), 4.30 - 4.50, 5.10 - 5.30 (1H, m), 6.62 (1H, d, J=8.5 Hz), 6.90 - 7.15 (1H, m), 7.25 - 7.60 (5H, m), 7.65 - 7.90 (5H, m), 8.00 - 8.30 (2H, m), 8.72 (1H, s)

Using the suitable starting compounds, there is obtained the  
20 compound of Example 141 in the same manner as in Example 162.

#### Example 163

To a solution of 7-chloro-5-(2-phthalimidoethyl)-1-[6-(2-chlorobenzoylamino)nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (1.8 g) in ethanol (50 ml) is added hydrazine monohydrate (0.19 ml), and the mixture is refluxed  
25 for 4 hours. The mixture is cooled, and thereto is added water. The mixture is extracted with dichloromethane, and the extract is washed with water, dried over magnesium sulfate, and evaporated under reduced pressure to remove the solvent. The residue is purified by silica gel column chromatography to give 7-chloro-5-(2-aminoethyl)-1-[6-(2-chlorobenzoylamino)nicotinoyl]-2,3,4,5-  
30 tetrahydro-1H-benzazepine (0.5 g) as colorless amorphous.

- 121 -

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  : 1.20 - 2.30 (6H, m), 2.60 - 3.40 (4H, m), 4.25 - 4.45, 5.05 - 5.25 (1H, m), 6.56 - 6.65 (1H, m), 6.90 - 7.05 (1H, m), 7.20 - 7.60 (5H, m), 7.69 (1H, d,  $J=6.4$  Hz), 8.05 - 8.25 (2H, m), 9.02 (1H, brs)

Using the suitable starting compounds, there is obtained the compound of Example 142 in the same manner as in Example 163.

#### Example 164

To a solution of 7-chloro-5-(2-aminoethyl)-1-[6-(2-chlorobenzoylamino)nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (0.5 g) in methanol (20 ml) is added 37 % formalin (1.4 ml), and thereto is added sodium cyanoborohydride (0.2 g), and further thereto is added with stirring acetic acid (0.9 ml) at 10°C, and the mixture is stirred at room temperature for 3 hours. The mixture is poured into ice-water, and the mixture is made basic with potassium carbonate, and the mixture is extracted with dichloromethane. The extract is washed with water, dried over magnesium sulfate, and evaporated under reduced pressure to remove the solvent. The residue is purified by silica gel column chromatography to give 7-chloro-5-(2-dimethylaminoethyl)-1-[6-(2-chlorobenzoylamino)nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (0.37 g) as colorless amorphous.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  : 1.20 - 2.80 (8H, m), 2.22, 2.26 (6H, s), 3.05 - 3.40 (2H, m), 4.25 - 4.44, 5.10 - 5.20 (1H, m), 6.50 - 6.65 (1H, m), 6.90 - 7.05 (1H, m), 7.20 - 7.30 (1H, m), 7.30 - 7.60 (4H, m), 7.71 (1H, d,  $J=6.3$  Hz), 8.15 - 8.20 (2H, m), 8.73 (1H, s)

Using the suitable starting compounds, there are obtained the compounds of Examples 130 and 139 in the same manner as in Example 164.

#### Example 165

To a solution of 7-chloro-5-(2-aminoethyl)-1-[6-(2-methylbenzoylamino)nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (0.42 g) in pyridine (10 ml) is added acetic anhydride (0.13 ml), and the mixture is stirred at 80°C for 2 hours, and then stirred at room temperature overnight. Water is added to the reaction solution, and the mixture is extracted with dichloromethane. The

- 122 -

extract is washed successively with diluted hydrochloric acid, water, and aqueous sodium hydrogen carbonate solution, dried over magnesium sulfate, and evaporated under reduced pressure to remove the solvent. The residue is purified by silica gel column chromatography to give 7-chloro-5-(2-acetylamin-  
ethyl)-1-[6-(2-methylbenzoylamino)nicotinoyl]-2,3,4,5-tetrahydro-1H-  
benzazepine (91 mg) as white powder.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  : 1.20 - 2.30 (6H, m), 1.99 (3H, s), 2.50 (3H, s), 2.80 - 3.60 (4H, m), 4.30 - 4.50, 5.05 - 5.25 (1H, m), 5.45 - 5.80 (1H, m), 6.55 - 6.65 (1H, m), 6.95 - 7.05 (1H, m), 7.20 - 7.60 (6H, m), 8.00 - 8.30 (3H, m)

#### 10      Example 166

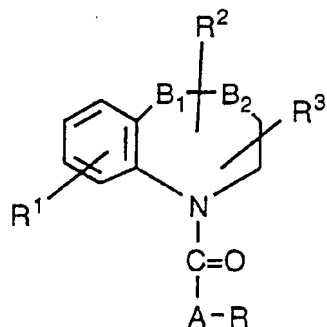
To a solution of 7-chloro-4,4-dimethoxy-1-[6-(2-methylbenzoylamino)nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine (1 g) in acetone (10 ml) is added 1N hydrochloric acid (5 ml), and the mixture is stirred at room temperature for 6 hours. Water is added to the reaction solution, and the  
mixture is neutralized with aqueous sodium hydroxide solution, and extracted  
with dichloromethane. The extract is washed with water, dried over  
magnesium sulfate, and evaporated under reduced pressure to remove the  
solvent. The residue is purified by silica gel column chromatography to give 7-  
chloro-4-oxo-1-[6-(2-methylbenzoylamino)nicotinoyl]-2,3,4,5-tetrahydro-1H-  
benzazepine (0.92 g) as colorless amorphous.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  : 2.50 (3H, s), 2.65 - 3.00 (2H, m), 3.40 - 3.70 (2H, m), 4.00 - 4.30 (1H, m), 4.65 - 5.00 (1H, m), 6.73 (1H, d,  $J=8.4$  Hz), 7.11 (1H, dd,  $J=2.4, 8.4$  Hz), 7.20 - 7.65 (6H, m), 8.07 (1H, d,  $J=1.7$  Hz), 8.24 (1H, d,  $J=8.7$  Hz), 8.50 (1H, s)

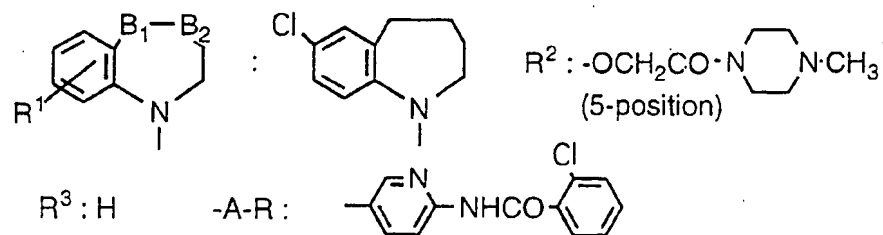
#### 25      Examples 167 - 198

Using the suitable starting compounds, the following compounds listed in Table 3 are obtained in the same manner as in Examples 1 and 17. Table 4 shows the NMR analysis of these compounds.

-123-

Table 3**Example 167**

Structure:



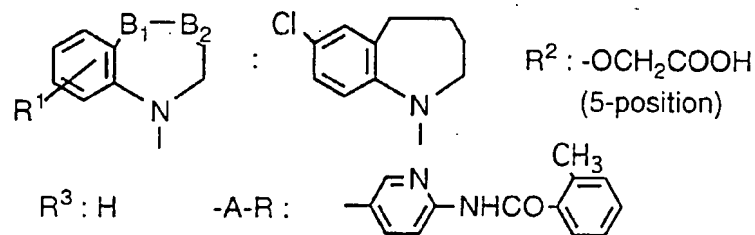
Crystalline Form: Colorless amorphous

NMR analysis: 57)

Form: Free

**Example 168**

Structure:



Crystalline Form: White powder

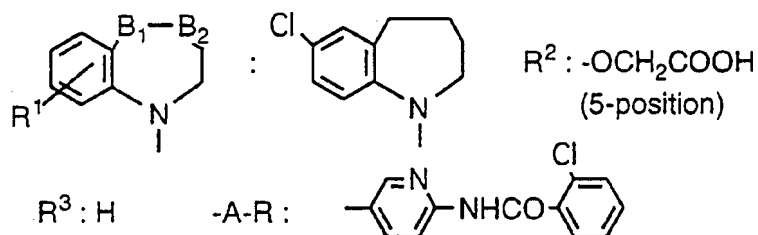
Recrystallization solvent: Diethyl ether-dichloromethane

Melting point: 220-222°C

Form: Free

## Example 169

Structure:



Crystalline Form: White powder

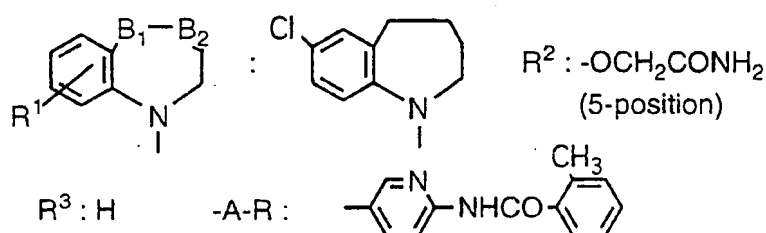
Recrystallization solvent: Dichloromethane-diethyl ether

Melting point: 223-225°C

Form: Free

## Example 170

Structure:



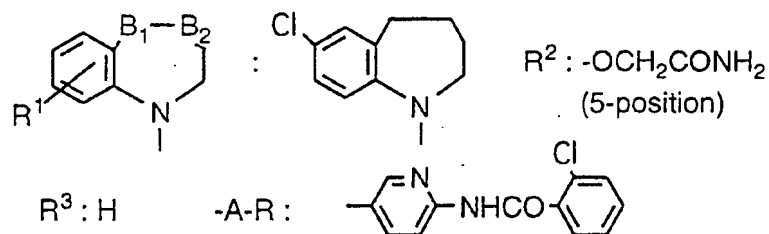
Crystalline Form: Colorless amorphous

NMR analysis: 58)

Form: Free

## Example 171

Structure:



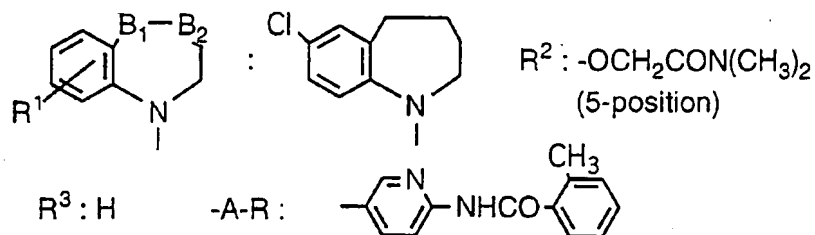
Crystalline Form: Colorless amorphous

NMR analysis: 59)

Form: Free

## Example 172

Structure:



Crystalline Form: White powder

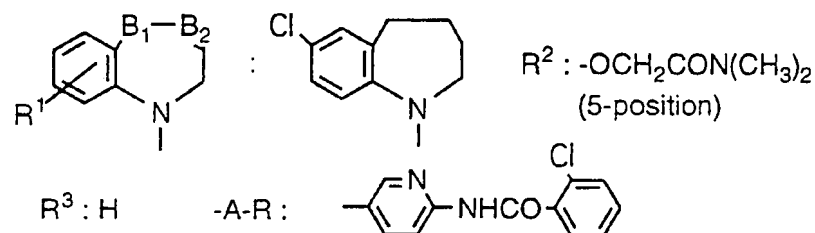
Recrystallization solvent: Dichloromethane-diethyl ether

Melting point: 107-110°C

Form: Free

## Example 173

Structure:



Crystalline Form: White powder

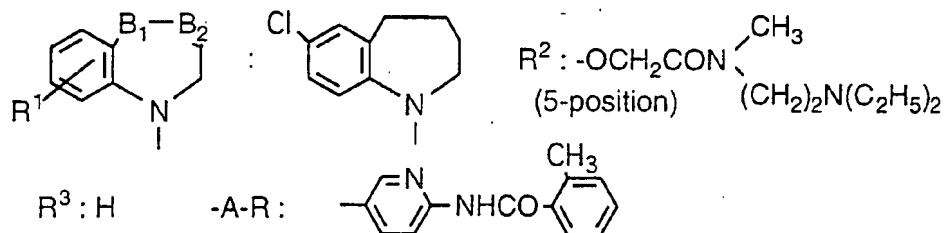
Recrystallization solvent: Dichloromethane-diethyl ether

Melting point: 119-122°C

Form: Free

## Example 174

Structure:



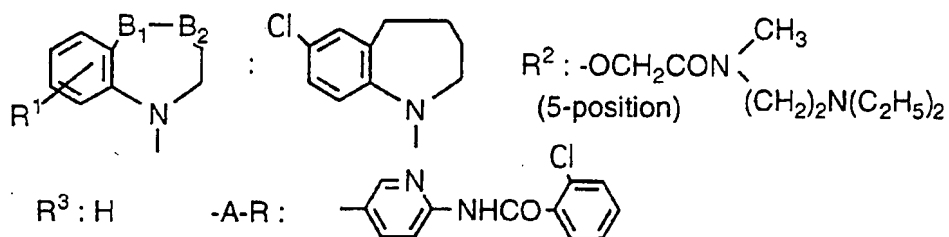
Crystalline Form: Colorless amorphous

NMR analysis: 60)

Form: Free

## Example 175

Structure:



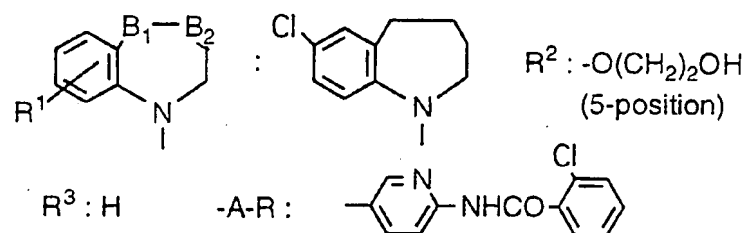
Crystalline Form: Colorless amorphous

NMR analysis: 61)

Form: Free

## Example 176

Structure:



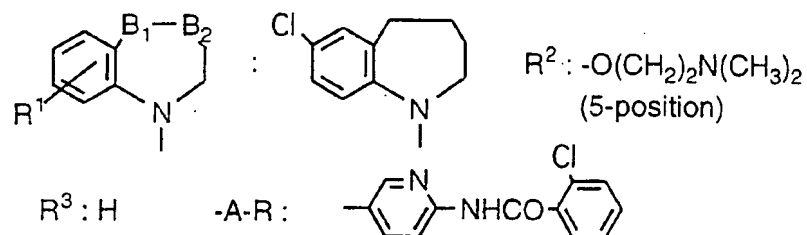
Crystalline Form: Colorless amorphous

NMR analysis: 62)

Form: Free

## Example 177

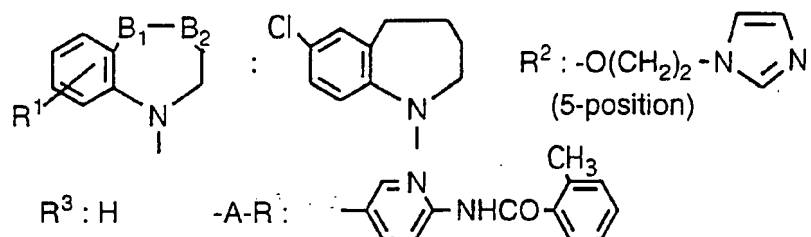
Structure:





## Example 178

Structure:



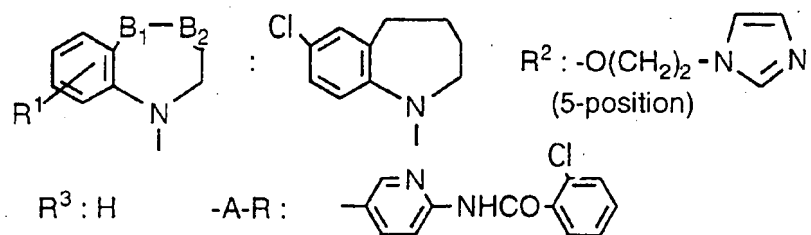
Crystalline Form: Colorless amorphous

NMR analysis: 63)

Form: Free

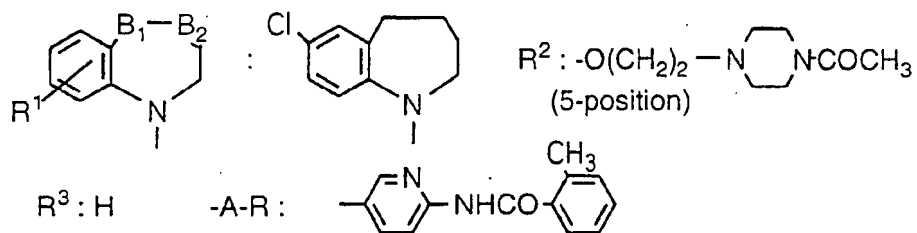
## Example 179

Structure:



## Example 180

Structure:



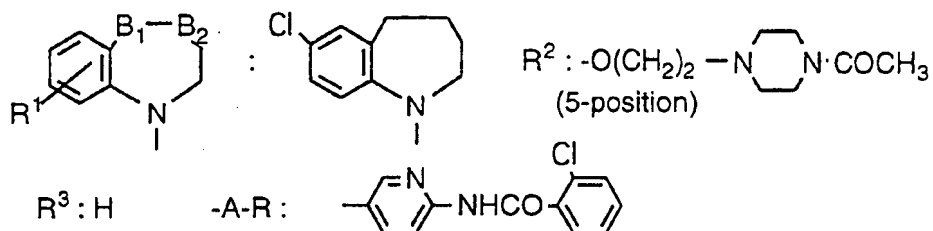
Crystalline Form: Colorless amorphous

NMR analysis: 64)

Form: Free

## Example 181

Structure:

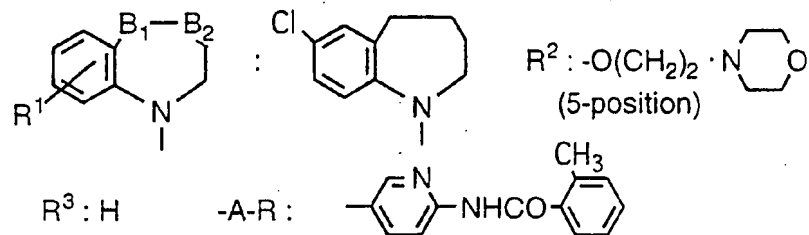


Crystalline Form: Colorless amorphous

NMR analysis: 65) Form: Free

## Example 182

Structure:

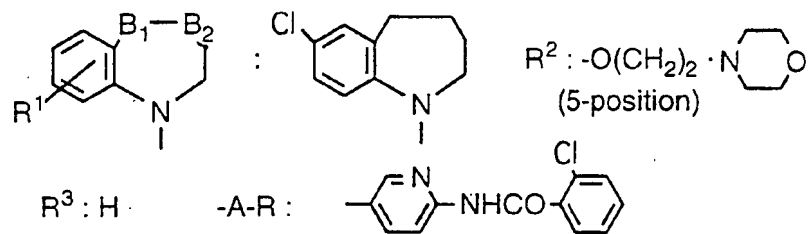


Crystalline Form: Colorless amorphous

NMR analysis: 66) Form: Free

## Example 183

Structure:

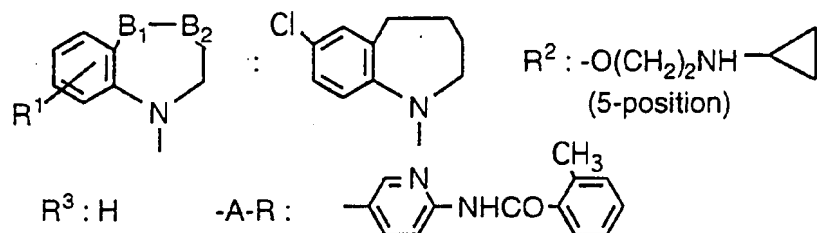


Crystalline Form: Colorless amorphous

NMR analysis: 67) Form: Free

## Example 184

Structure:



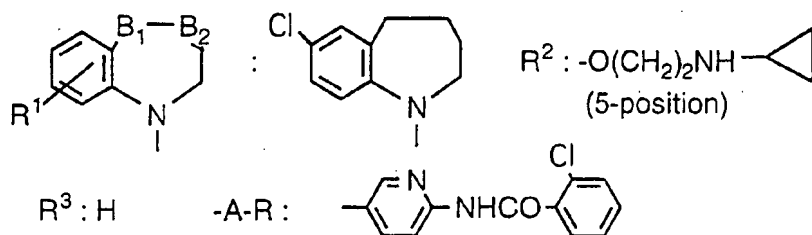
Crystalline Form: Colorless amorphous

NMR analysis: 68)

Form: Free

## Example 185

Structure:



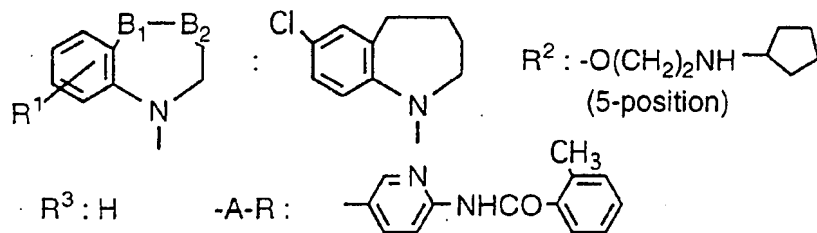
Crystalline Form: Yellow amorphous

NMR analysis: 69)

Form: Free

## Example 186

Structure:



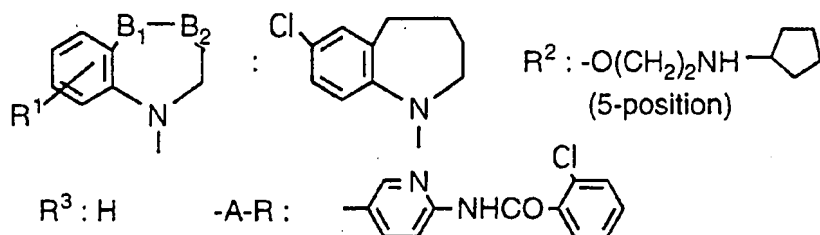
Crystalline Form: Brown amorphous

NMR analysis: 70)

Form: Free

## Example 187

Structure:



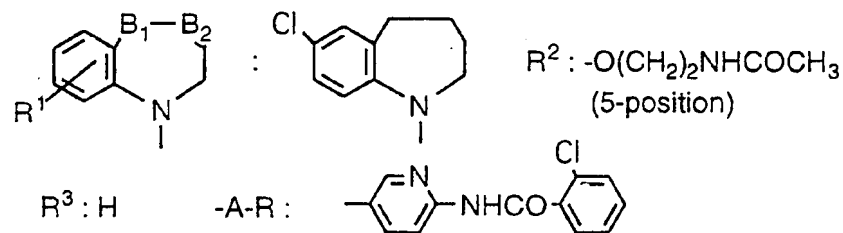
Crystalline Form: Brown amorphous

NMR analysis: 71)

Form: Free

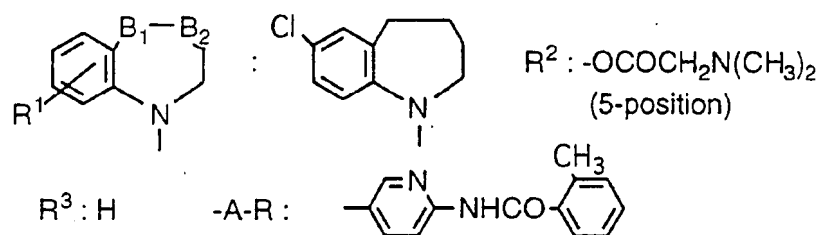
## Example 188

Structure:



## Example 189

Structure:



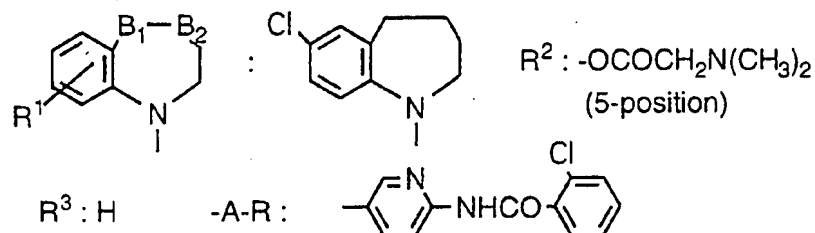
Crystalline Form: Colorless amorphous

NMR analysis: 72)

Form: 2 HCl

## Example 190

Structure:



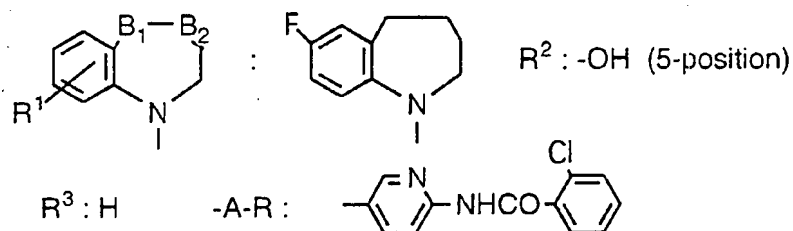
Crystalline Form: Colorless amorphous

NMR analysis: 73)

Form: Free

## Example 191

Structure:



Crystalline Form: White powder

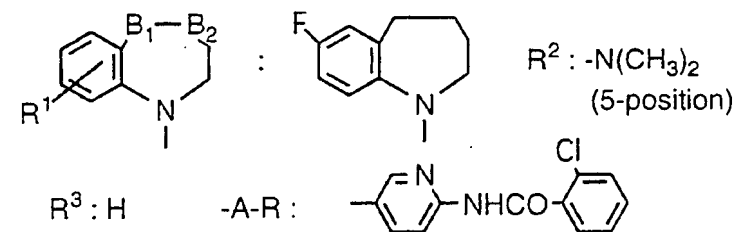
Recrystallization solvent: Diethyl ether

Melting point: 115-118°C.

Form: Free

## Example 192

Structure:



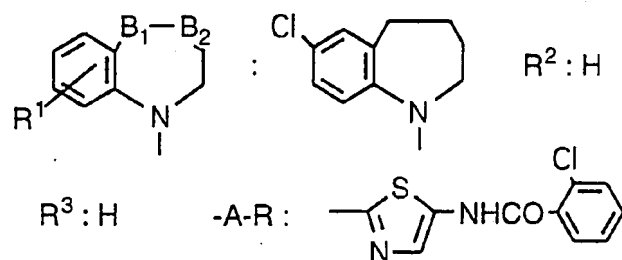
Crystalline Form: Colorless oil

NMR analysis: 74)

Form: Free

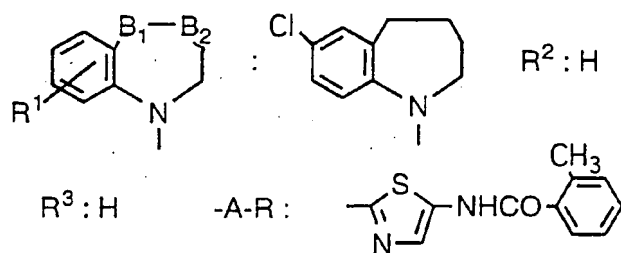
## Example 193

Structure:



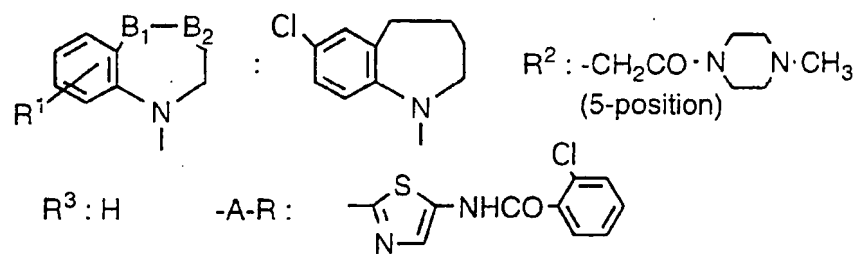
## Example 194

Structure:



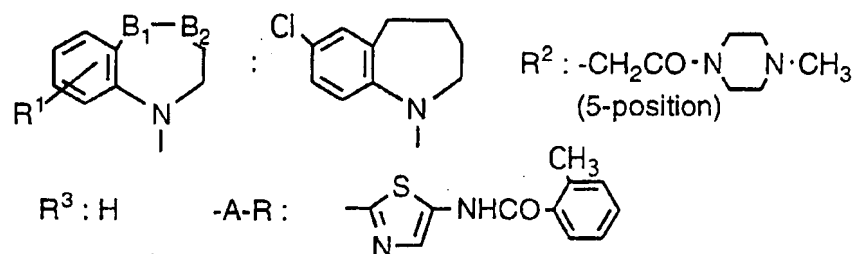
## Example 195

Structure:



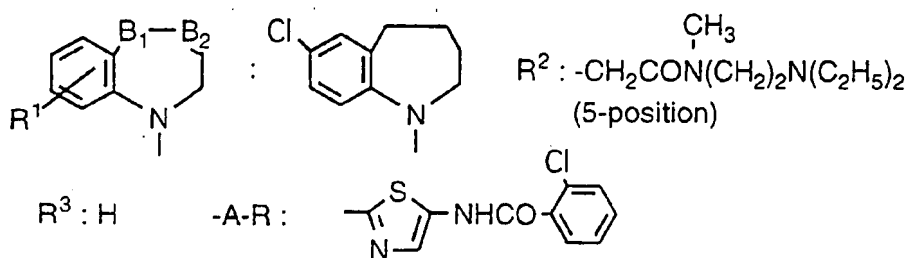
## Example 196

Structure:



## Example 197

Structure:



## Example 198

Structure:

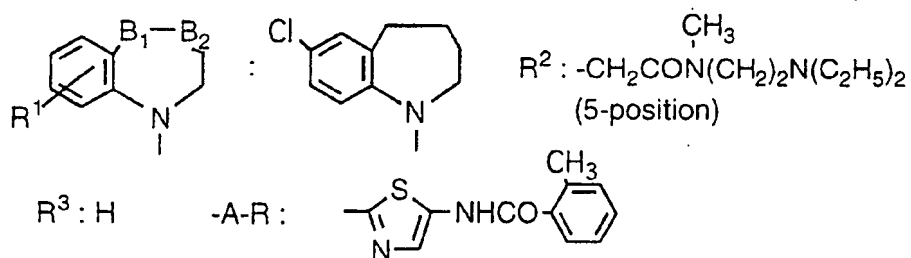


Table 4

- 57)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  : 1.60 - 1.90 (2H, m), 2.30 - 2.65 (9H, m), 2.70 - 3.05 (1H, m), 3.45 - 3.80 (4H, m), 4.20 - 5.20 (4H, m), 6.55 - 6.70 (1H, m), 7.00 - 7.15 (1H, m), 7.30 - 7.50 (3H, m), 7.50 - 7.85 (3H, m), 8.20 - 8.30 (2H, m), 8.86 (1H, s)
- 58)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  : 1.60 - 2.60 (4H, m), 2.50 (3H, s), 2.70 - 3.05 (1H, m), 4.00 - 4.20 (2H, m), 4.50 - 5.15 (2H, m), 5.70 - 6.80 (2H, m), 6.60 - 6.80 (1H, m), 7.00 - 7.75 (7H, m), 8.00 - 8.30 (2H, m), 8.53 (1H, s)
- 59)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  : 1.60 - 2.55 (4H, m), 2.70 - 3.05 (1H, m), 3.90 - 4.25 (2H, m), 4.50 - 5.15 (2H, m), 5.85 - 6.80 (2H, m), 6.55 - 6.80 (1H, m), 7.00 - 7.20 (1H, m), 7.25 - 7.55 (4H, m), 7.55 - 7.75 (2H, m), 8.00 - 8.30 (2H, m), 8.99 (1H, s)
- 60)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  : 0.85 - 1.15 (6H, m), 1.55 - 1.90 (2H, m), 2.25 - 2.70 (11H, m), 2.70 - 3.15 (4H, m), 3.20 - 3.65 (2H, m), 4.15 - 5.20 (4H, m), 6.55 - 6.70 (1H, m), 7.00 - 7.15 (1H, m), 7.20 - 7.85 (6H, m), 8.05 - 8.35 (2H, m), 8.35 - 8.50 (1H, m)
- 61)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  : 0.85 - 1.15 (6H, m), 1.55 - 1.90 (2H, m), 2.30 - 2.70 (8H, m), 2.70 - 3.15 (4H, m), 3.20 - 3.65 (2H, m), 4.15 - 5.20 (4H, m), 6.55 - 6.75 (1H, m), 6.95 - 7.15 (1H, m), 7.30 - 7.55 (3H, m), 7.55 - 7.85 (3H, m), 8.10 - 8.35 (2H, m), 8.75 - 8.95 (1H, m)
- 62)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  : 1.50 - 2.55 (4H, m), 2.70 - 3.00 (1H, m), 3.50 - 4.00 (4H, m), 4.50 - 5.10 (2H, m), 6.61 (1H, d,  $J=8.1$  Hz), 7.00 - 7.15 (1H, m), 7.25 - 7.85 (6H, m), 8.05 - 8.35 (2H, m), 8.85 (1H, s)
- 63)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  : 1.50 - 2.60 (4H, m), 2.51 (3H, s), 2.65 - 3.05 (1H, m), 3.70 - 4.05 (2H, m), 4.05 - 5.20 (4H, m), 6.55 - 6.70 (1H, m), 6.90 - 7.80 (10H, m), 8.05 - 8.25 (2H, m), 8.52, 8.61 (1H, s)
- 64)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  : 1.60 - 1.90 (2H, m), 2.01, 2.06 (3H, s), 1.90 - 3.00 (9H, m), 2.50 (3H, s), 3.30 - 3.85 (6H, m), 4.45 - 5.15 (2H, m), 6.62 (1H, d,  $J=8.3$



- 135 -

Hz), 7.04 (1H, d, J=8.2 Hz), 7.20 - 7.85 (6H, m), 8.05 - 8.35 (2H, m), 8.52, 8.57 (1H, s)

65)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.55 - 3.00 (11H, m), 2.02, 2.10 (3H, s), 3.30 - 3.85 (6H, m), 4.40 - 5.15 (2H, m), 6.62 (1H, d, J=8.1 Hz), 7.04 (1H, d, J=8.3 Hz),  
5 7.35 - 7.90 (6H, m), 8.10 - 8.40 (2H, m), 8.76, 8.80 (1H, s)

66)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.55 - 3.00 (11H, m), 2.50 (3H, s), 3.55 - 3.90 (6H, m), 4.45 - 5.15 (2H, m), 6.61 (1H, d, J=8.2 Hz), 7.03 (1H, d, J=8.2 Hz), 7.20 - 7.85 (6H, m), 8.05 - 8.35 (2H, m), 8.51 (1H, s)

67)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.55 - 3.00 (11H, m), 3.55 - 3.90 (6H, m), 4.45 -  
10 5.15 (2H, m), 6.61 (1H, d, J=8.3 Hz), 7.03 (1H, d, J=8.2 Hz), 7.30 - 7.85 (6H, m), 8.10 - 8.35 (2H, m), 8.75, 8.80 (1H, s)

68)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 0.20 - 0.60 (4H, m), 1.55 - 2.65 (5H, m), 2.50 (3H, s), 2.65 - 3.10 (3H, m), 3.50 - 3.85 (2H, m), 4.40 - 5.15 (2H, m), 6.62 (1H, d, J=8.2 Hz), 7.04 (1H, d, J=8.1 Hz), 7.20 - 7.80 (6H, m), 8.09 - 8.40 (3H, m)

69)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 0.20 - 0.60 (4H, m), 1.50 - 2.60 (5H, m), 2.65 -  
15 3.10 (3H, m), 3.50 - 3.80 (2H, m), 4.45 - 5.15 (2H, m), 6.61 (1H, d, J=8.4 Hz), 7.04 (1H, d, J=6.9 Hz), 7.30 - 7.85 (6H, m), 8.05 - 8.35 (2H, m), 8.78 (1H, s)

70)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.05 - 2.20 (12H, m), 2.20 - 2.60 (1H, m), 2.50 (3H, s), 2.70 - 3.05 (3H, m), 3.50 - 3.90 (2H, m), 4.45 - 5.15 (2H, m), 6.55 - 6.70 (1H, m), 7.04 (1H, d, J=8.4 Hz), 7.20 - 7.80 (6H, m), 8.05 - 8.30 (2H, m), 8.35 -  
20 8.50 (1H, m)

71)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.05 - 2.60 (12H, m), 2.65 - 3.30 (4H, ), 2.50 - 3.85 (2H, m), 4.45 - 5.10 (2H, m), 6.55 - 6.70 (1H, m), 7.04 (1H, d, J=8.0 Hz), 7.30 - 7.80 (6H, m), 8.10 - 8.33 (2H, m), 8.60 - 8.90 (1H, m)

72)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.60 - 2.45 (4H, m), 2.30 - 2.40 (3H, m), 2.70 -  
25 3.10 (7H, m), 4.10 - 5.00 (3H, m), 6.05 - 6.20 (1H, m), 6.95 (1H, d, J=8.2 Hz), 7.15 - 7.60 (6H, m), 7.70 - 7.90 (1H, m), 8.03 (1H, d, J=8.6 Hz), 8.20 (1H, s), 11.04 (1H, s), 11.28, 11.85 (1H, s)

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73)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  : 2.34, 2.43 (6H, s), 1.70 - 2.65 (5H, m), 2.70 - 3.00 (1H, m), 3.40 (2H, s), 4.70 - 5.15 (1H, m), 6.00 - 6.20 (1H, m), 6.55 - 6.70 (1H, m), 7.00 - 7.15 (1H, m), 7.30 - 7.45 (3H, m), 7.50 - 7.70 (2H, m), 8.05 - 8.25 (2H, m), 9.15 - 9.50 (1H, br)

5        74)  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  : 1.16 - 2.57 (4H, m), 2.15, 2.40 (total, 6H, s), 2.61 - 3.63 (2H, m), 4.03 - 5.09 (1H, m), 6.53 - 8.26 (10H, m), 8.36, 8.77 (total, 1H, brs)

#### Pharmacological Test

##### Experiment 1 : $V_1$ receptor binding assay

10        Using rat liver plasma membrane preparations prepared according to Ichihara's method [cf: Akira Ichihara, J. Bio. Chem., 258, 9283 (1983)], the plasma membrane (50000 dpm,  $2 \times 10^{-10}$  M) of [ $^3\text{H}$ ]-Arg-vasopressin and a test compound (60  $\mu\text{g}$ ,  $10^{-8}$  to  $10^{-4}$  M) are incubated at  $37^\circ\text{C}$  for 10 minutes in 100 mM Tris-HCl buffer (pH: 8.0) (250  $\mu\text{l}$ ) containing 5 mM  $\text{MgCl}_2$ , 1 mM EDTA and

15        0.1 % BSA. After incubation, the mixture is filtered three times using the glass filter (GF/F) so as to separate the membrane preparation binding with vasopressin and then washed with the buffer (5 ml). This glass filter is taken out and mixed with liquid scintillation cocktail. The amount of [ $^3\text{H}$ ]-vasopressin binding with the membrane is measured by liquid scintillation counter and the

20        rate of the inhibitory effect of the test compound is estimated according to the following equation.

$$\text{Rate of the inhibitory effect (\%)} = 100 - \frac{C_1 - B_1}{C_0 - B_1} \times 100$$

25         $C_1$ : The amount of [ $^3\text{H}$ ]-vasopressin binding with the membrane in the presence of the test compound (known amount)

$C_0$ : The amount of [ $^3\text{H}$ ]-vasopressin binding with the membrane in the absence of the test compound

$B_1$ : The amount of [ $^3\text{H}$ ]-vasopressin binding with the membrane in

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the presence of the excess amount of vasopressin ( $10^{-6}$  M)

The results are expressed as  $IC_{50}$  value, which is the concentration of the test compound required to achieve the inhibitory effect in the rate of 50 %.

5 The results are shown in the following Table 5.

Experiment 2 :  $V_2$  receptor binding assay

Using rat kidney plasma membrane preparations prepared according to O. Hechter's method [cf: J. Bio. Chem., 253, 3211 (1978)], the plasma membrane (100000 dpm,  $4 \times 10^{-10}$  M) of [ $^3H$ ]-Arg-vasopressin and a test  
 10 compound (0.6 mg,  $10^{-10}$  to  $10^{-5}$  M) are incubated at  $4^\circ C$  for 3 hours in 100 mM Tris-HCl buffer (pH: 8.0) (250  $\mu$ l) containing 5 mM  $MgCl_2$ , 1 mM EDTA and 0.1 % BSA. After incubation, the mixture is filtered using the glass filter (GF/F) so as to separate the membrane preparation binding with vasopressin and then washed twice with the buffer (each 5 ml). This glass filter is taken out and  
 15 mixed with liquid scintillation cocktail. The amount of [ $^3H$ ]-vasopressin binding with the membrane is measured by liquid scintillation counter and the rate of the inhibitory effect of the test compound is estimated according to the following equation.

$$20 \quad \text{Rate of the inhibitory effect (\%)} = 100 - \frac{C_1 - B_1}{C_0 - B_1} \times 100$$

$C_1$ : The amount of [ $^3H$ ]-vasopressin binding with the membrane in the presence of the test compound (known amount)

$C_0$ : The amount of [ $^3H$ ]-vasopressin binding with the membrane in  
 25 the absence of the test compound

$B_1$ : The amount of [ $^3H$ ]-vasopressin binding with the membrane in the presence of the excess amount of vasopressin ( $10^{-6}$  M)

The results are expressed as  $IC_{50}$  value, which is the concentration of the test compound required to achieve the inhibitory effect in the rate of 50 %.

The results are shown in the following Table 5.

Table 5

Test compound No		IC <sub>50</sub> (μM) in V <sub>1</sub> receptor binding assay	IC <sub>50</sub> (μM) in V <sub>2</sub> receptor binding assay
5	Compound of Ex. 25	0.014	0.004
	Compound of Ex. 26	0.078	0.021
	Compound of Ex. 28	0.077	0.17
	Compound of Ex. 29	0.024	0.011
	Compound of Ex. 31	0.057	0.12
10	Compound of Ex. 32	0.012	0.016
	Compound of Ex. 33	0.007	0.003
	Compound of Ex. 34	0.066	0.016
	Compound of Ex. 35	0.020	0.007
	Compound of Ex. 36	0.043	0.003
15	Compound of Ex. 37	0.011	0.005
	Compound of Ex. 38	0.026	0.003
	Compound of Ex. 39	0.91	0.068
	Compound of Ex. 40	0.044	0.009
	Compound of Ex. 41	0.022	0.004
20	Compound of Ex. 42	0.030	0.003
	Compound of Ex. 43	0.013	0.010
	Compound of Ex. 44	0.008	0.011
	Compound of Ex. 45	0.005	0.007
	Compound of Ex. 47	0.15	0.089
25	Compound of Ex. 48	0.067	0.30
	Compound of Ex. 49	0.041	0.25
	Compound of Ex. 50	0.078	0.061
	Compound of Ex. 52	0.051	0.022
	Compound of Ex. 53	0.055	0.019

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5	Compound of Ex. 73	0.012	0.0019
	Compound of Ex. 76	0.027	0.008
	Compound of Ex. 78	0.017	0.010
	Compound of Ex. 79	0.041	0.0037
	Compound of Ex. 83	0.071	0.43
10	Compound of Ex. 88	0.026	0.20
	Compound of Ex. 92	0.060	0.38
	Compound of Ex. 94	0.042	0.036
	Compound of Ex. 96	0.043	0.30
	Compound of Ex. 97	0.005	0.16
15	Compound of Ex. 101	0.49	0.033
	Compound of Ex. 104	0.038	0.024
	Compound of Ex. 105	0.009	0.003
	Compound of Ex. 112	0.009	0.003
	Compound of Ex. 114	0.011	0.003
20	Compound of Ex. 116	0.012	0.0031
	Compound of Ex. 122	0.015	0.003
	Compound of Ex. 123	0.020	0.0032
	Compound of Ex. 126	0.019	0.0053
	Compound of Ex. 127	0.029	0.0059
25	Compound of Ex. 128	0.016	0.0046
	Compound of Ex. 129	0.031	0.0048
	Compound of Ex. 139	0.016	0.0041
	Compound of Ex. 140	0.031	0.0056
	Compound of Ex. 143	0.0066	0.0031
	Compound of Ex. 148	0.027	0.017
	Compound of Ex. 173	0.024	0.0053
	Compound of Ex. 175	0.0084	0.0027
	Compound of Ex. 171	0.0071	0.0031

5	Compound of Ex. 169	0.117	0.019
	Compound of Ex. 178	0.029	0.0080
	Compound of Ex. 182	0.028	0.010
	Compound of Ex. 187	0.0078	0.0080
	Compound of Ex. 181	0.015	0.0044
	Compound of Ex. 189	0.034	0.012

### Experiment 3: Oxytocin receptor binding assay

According to the method of W. Y. Chan et al. [Endocrinology, 126, 2095-2101 (1990)], uterine muscle is taken out from a rat which has previously been injected subcutaneously with diethylstilbestrol the day before, and homogenized, which is used as a membrane preparation. The membrane preparation (0.2 mg), [<sup>3</sup>H]-oxytocin (100000 dpm, 10<sup>-9</sup> M), a test compound (10<sup>-9</sup> - 10<sup>-5</sup> M) are incubated at 25°C for one hour in 100 mM Tris-HCl buffer (pH 8.0, 250 µl) containing a 5 mM MgCl<sub>2</sub>, 1 mM MEDTA and 0.1 % BSA. The mixture is filtered through the glass filter (GF/B) so as to separate the membrane preparation binding with [<sup>3</sup>H]-oxytocin, and then, washed twice with the buffer (5 ml). This glass filter is put into a vial and mixed with Aquasole (liquid scintillation cocktail). The amount of [<sup>3</sup>H]-oxytocin binding with the membrane is measured by liquid scintillation counter. The rate of the inhibitory effect of the test compound is estimated according to the following equation.

$$\text{Inhibitory Rate (\%)} = 100 - [(C_1 - B)/(C_0 - B)] \times 100$$

C<sub>1</sub>: The amount of [<sup>3</sup>H]-oxytocin binding with the membrane in the presence of a test compound (known amount)

C<sub>0</sub>: The amount of [<sup>3</sup>H]-oxytocin binding with the membrane in the absence of a test compound

B: The amount of [<sup>3</sup>H]-oxytocin binding with the membrane in the presence of the excess amount of oxytocin (5 x 10<sup>-6</sup> M).

The results are expressed as IC<sub>50</sub> value, which is the concentration

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of the test compound required to achieve the inhibitory rate in the rate of 50 %.

The results are shown in the following Table 6.

Table 6

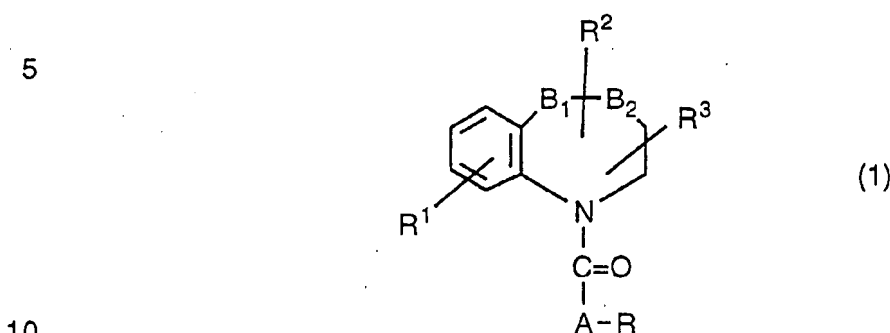
	Test compound No.	IC <sub>50</sub> (μM)	Test Compound No.	IC <sub>50</sub> (μM)
5	Compound of Ex. 37	1.14	Compound of Ex. 40	0.74
	Compound of Ex. 44	0.307	Compound of Ex. 45	0.26
	Compound of Ex. 46	0.36	Compound of Ex. 43	0.29
	Compound of Ex. 52	1.6	Compound of Ex. 72	0.44
	Compound of Ex. 76	1.5	Compound of Ex. 77	1.8
10	Compound of Ex. 80	1.0	Compound of Ex. 82	9.7
	Compound of Ex. 83	6.6	Compound of Ex. 86 *	17 %
	Compound of Ex. 88	4.5	Compound of Ex. 89	7.3
	Compound of Ex. 91*	38 %	Compound of Ex. 92*	38 %
	Compound of Ex. 97	1.8	Compound of Ex. 94	0.84
15	Compound of Ex. 104	0.51	Compound of Ex. 107	0.41
	Compound of Ex. 112	0.28	Compound of Ex. 114	0.32
	Compound of Ex. 101	3.5	Compound of Ex. 120	0.35
	Compound of Ex. 122	0.64	Compound of Ex. 145	1.2
	Compound of Ex. 123	0.32	Compound of Ex. 126	1.32
20	Compound of Ex. 127	0.68		

\*): Inhibitory Rate (%) at 10<sup>-5</sup> M

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## CLAIMS

1. A benzoheterocyclic compound of the formula (1):



wherein R<sup>1</sup> is hydrogen atom or a halogen atom,

R<sup>2</sup> is hydrogen atom, oxo group, a lower alkylidene group, hydroxy group, a lower alkoxy group, a lower alkenyloxy group, a hydroxy-substituted lower alkoxy group, a lower alkoxycarbonyl-substituted lower alkoxy group, a carboxy-substituted lower alkoxy group, a lower alkylsulfonyloxy-substituted lower alkoxy group, a phthalimide-substituted lower alkoxy group, a hydroxy-substituted lower alkyl group, a group of the formula: -O-D-(CO)<sub>l</sub>NR<sup>4</sup>R<sup>5</sup>

(wherein D is a lower alkylene group, l is 0 or 1, R<sup>4</sup> and R<sup>5</sup> are the same or different and are hydrogen atom, a lower alkyl group, a lower alkanoyl group, a cycloalkyl group, or an amino-substituted lower alkyl group which may optionally have a lower alkyl substituent, or R<sup>4</sup> and R<sup>5</sup> may combine together with the nitrogen atom to which they bond to form a 5- or 6-membered saturated heterocyclic group which may be intervened or not with a nitrogen atom, an oxygen atom or a sulfur atom, wherein said heterocyclic group may optionally be substituted by a lower alkyl group or a lower alkanoyl group), a group of the formula: -E-(CO)<sub>l</sub>NR<sup>6</sup>R<sup>7</sup> (wherein l is the same as defined above, E is a lower alkylene group, R<sup>6</sup> and R<sup>7</sup> are the same or different and are hydrogen atom, a lower alkyl group, an amino-substituted lower alkyl group which may optionally have a lower alkyl substituent, or a lower alkanoyl group,



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or R<sup>6</sup> and R<sup>7</sup> may combine together with the nitrogen atom to which they bond to form a 5- or 6-membered saturated heterocyclic group which may be intervened or not with a nitrogen atom, an oxygen atom or a sulfur atom, wherein said heterocyclic group may optionally be substituted by a lower alkyl group, a lower alkanoyl group or a lower alkoxy carbonyl group), a lower alkanoyloxy-substituted lower alkyl group, a lower alkoxy carbonyl-substituted lower alkyl group, an amino which may optionally be substituted by a lower alkyl group or a cycloalkyl group, a carboxy-substituted lower alkyl group, a lower alkylsulfonyloxy-substituted lower alkyl group, a phthalimide-substituted lower alkyl group, an imidazolyl-substituted lower alkyl group, a 1,2,4-triazolyl-substituted lower alkyl group, an amino-substituted lower alkanoyloxy group which may optionally have a lower alkyl substituent, or an imidazolyl-substituted lower alkoxy group,

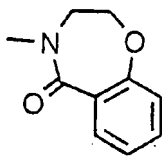
R<sup>3</sup> is hydrogen atom, a lower alkoxy group or a hydroxy-substituted lower alkyl group,

B<sub>1</sub> and B<sub>2</sub> are each methylene group or a group of the formula: -NR<sup>8</sup>.

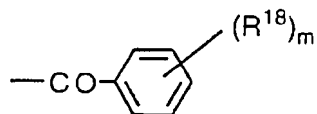
(wherein R<sup>8</sup> is hydrogen atom or a lower alkyl group),

A is a 5- or 6-membered unsaturated heterocyclic residue having 1 to 2 heteroatoms selected from an oxygen atom, a nitrogen atom and a sulfur atom, and

R is a group of the formula: -NHRA or a group of the formula:



wherein R<sup>A</sup> is a group of the formula:



[wherein m is an integer of 1 to 3, R<sup>18</sup> is hydrogen atom, a lower alkyl group, a

- 1 4 4 -

lower alkoxy group, a halogen atom, nitro group, a lower alkoxy carbonyl group, carboxy group, a lower alkoxy carbonyl-substituted lower alkoxy group, a hydroxy-substituted lower alkoxy group, a carboxy-substituted lower alkoxy group, a lower alkylsulfonyloxy-substituted lower alkoxy group, a phthalimide-substituted lower alkoxy group, or a group of the formula:  $-O-E-(CO)_lNR^{19}R^{20}$  (wherein E and l are the same as defined above,  $R^{19}$  and  $R^{20}$  are the same or different and are hydrogen atom or a lower alkyl group, or  $R^{19}$  and  $R^{20}$  may combine together with the nitrogen atom to which they bond to form a 5- or 6-membered saturated heterocyclic group which may be intervened or not with a nitrogen atom or an oxygen atom, wherein said heterocyclic group may optionally be substituted by a lower alkyl group, or an amino group which may optionally be substituted by a lower alkanoyl group)), thienylcarbonyl group, a cycloalkylcarbonyl group or a phenyl-lower alkanoyl group which may optionally have a lower alkyl substituent on the phenyl ring, or a salt thereof.

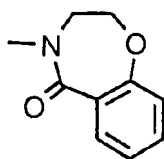
2. The benzoheterocyclic compound according to claim 1, wherein both  $B^1$  and  $B^2$  are methylene group, the unsaturated heterocyclic residue for A is imidazolyl, pyrrolyl, imidazoliny, pyridyl, pyrimidinyl, oxazolyl, pyrazolyl, pyrazoliny, thiazolyl, thiazoliny, thienyl, furyl, pyranly, isothiazolyl, isoxazolyl, pyrazinyl, pyridazinyl, pyrroliny, or a salt thereof.

3. The benzoheterocyclic compound according to claim 1, wherein one of  $B_1$  and  $B_2$  is methylene group and the other is a group of the formula:  $-NR^8-$  (wherein  $R^8$  is the same as defined above), and the unsaturated heterocyclic residue for A is imidazolyl, pyrrolyl, imidazoliny, pyridyl, pyrimidinyl, oxazolyl, pyrazolyl, pyrazoliny, thiazolyl, thiazoliny, thienyl, furyl, pyranly, isothiazolyl, isoxazolyl, pyrazinyl, pyridazinyl, pyrroliny, or a salt thereof.

4. The benzoheterocyclic compound according to claim 1, wherein both  $B_1$  and  $B_2$  are a group of the formula:  $-NR^8-$  (wherein  $R^8$  is the same as

defined above), and the unsaturated heterocyclic residue for A is imidazolyl, pyrrolyl, imidazoliny, pyridyl, pyrimidinyl, oxazolyl, pyrazolyl, pyrazolinyl, thiazolyl, thiazolinyl, thienyl, furyl, pyranyl, isothiazolyl, isoxazolyl, pyrazinyl, pyridazinyl, pyrrolinyl, or a salt thereof.

- 5                    5. The benzoheterocyclic compound according to claim 1, wherein R is a group of the formula:



- 10                    and the unsaturated heterocyclic residue for A is imidazolyl, pyrrolyl, imidazoliny, pyridyl, pyrimidinyl, oxazolyl, pyrazolyl, pyrazolinyl, thiazolyl, thiazolinyl, thienyl, furyl, pyranyl, isothiazolyl, isoxazolyl, pyrazinyl, pyridazinyl, pyrrolinyl, or a salt thereof.

- 15                    6. The benzoheterocyclic compound according to claim 1, wherein R<sup>3</sup> is a lower alkoxy group or a hydroxy-substituted lower alkyl group, or a salt thereof.

7. The benzoheterocyclic compound according to claim 2, wherein A is pyridyl group, or a salt thereof.

- 20                    8. The benzoheterocyclic compound according to claim 2, wherein A is thiazolyl group, or a salt thereof.

9. The benzoheterocyclic compound according to claim 2, wherein A is thienyl group or furyl group, and R is a group of the formula: -NHR<sup>A</sup> (R<sup>A</sup> is the same as defined in claim 1), or a salt thereof.

- 25                    10. The benzoheterocyclic compound according to claim 3, wherein A is pyridyl group, and R is a group of the formula: -NHR<sup>A</sup> (R<sup>A</sup> is the same as defined in claim 1), or a salt thereof.

- 30                    11. The benzoheterocyclic compound according to claim 3, wherein A is thiazolyl group, and R is a group of the formula: -NHR<sup>A</sup> (R<sup>A</sup> is the same as defined in claim 1), or a salt thereof.

12. The benzoheterocyclic compound according to claim 3, wherein A is thienyl group or furyl group, and R is a group of the formula: -NHR<sup>A</sup> (R<sup>A</sup> is the same as defined in claim 1), or a salt thereof.

13. The benzoheterocyclic compound according to claim 5, wherein A is pyridyl group, thiazolyl group, thienyl group or furyl group, and both B<sub>1</sub> and B<sub>2</sub> are methylene group, or a salt thereof.

14. The benzoheterocyclic compound according to claim 7, wherein R<sup>3</sup> is hydrogen atom, R is a group of the formula: -NHR<sup>A</sup> (R<sup>A</sup> is the same as defined in claim 1), R<sup>2</sup> is hydrogen atom, oxo group, a lower alkylidene group, a lower alkoxy group, a lower alkenyloxy group, a hydroxy-substituted lower alkoxy group, a lower alkoxycarbonyl-substituted lower alkoxy group, a carboxy-substituted lower alkoxy group, a lower alkylsulfonyloxy-substituted lower alkoxy group, a phthalimide-substituted lower alkoxy group, a group of the formula: -O-D-(CO)<sub>l</sub>NR<sup>4</sup>R<sup>5</sup> (wherein D is a lower alkylene group, l is 0 or 1, R<sup>4</sup> and R<sup>5</sup> are the same or different and are hydrogen atom, a lower alkyl group, a lower alkanoyl group, a cycloalkyl group, or an amino-substituted lower alkyl group which may optionally have a lower alkyl substituent, or R<sup>4</sup> and R<sup>5</sup> may combine together with the nitrogen atom to which they bond to form a 5- or 6-membered saturated heterocyclic group which may be intervened or not with a nitrogen atom, an oxygen atom or a sulfur atom, wherein said heterocyclic group may optionally be substituted by a lower alkyl group or a lower alkanoyl group), a lower alkanoyloxy-substituted lower alkyl group, a lower alkoxycarbonyl-substituted lower alkyl group, an amino which may optionally be substituted by a lower alkyl group or a cycloalkyl group, a lower alkylsulfonyloxy-substituted lower alkyl group, a phthalimide-substituted lower alkyl group, an imidazolyl-substituted lower alkyl group, a 1,2,4-triazolyl-substituted lower alkyl group, an amino-substituted lower alkanoyloxy group which may optionally have a lower alkyl substituent, or an imidazolyl-substituted lower alkoxy group, or a salt thereof.

15. The benzoheterocyclic compound according to claim 7, wherein  
R<sup>3</sup> is hydrogen atom, R is a group of the formula: -NHRA (R<sup>A</sup> is the same as  
defined in claim 1), R<sup>2</sup> is a group of the formula: -E-(CO)<sub>l</sub>NR<sup>6</sup>R<sup>7</sup> (wherein E and  
l are the same as defined in claim 1, R<sup>6</sup> and R<sup>7</sup> are the same or different and  
5 are hydrogen atom, a lower alkyl group, an amino-substituted lower alkyl group  
which may optionally have a lower alkyl substituent, or a lower alkanoyl group),  
or a salt thereof.

16. The benzoheterocyclic compound according to claim 7, wherein  
R<sup>3</sup> is hydrogen atom, R is a group of the formula: -NHRA (R<sup>A</sup> is the same as  
10 defined in claim 1), R<sup>2</sup> is a group of the formula: -E-(CO)<sub>l</sub>NR<sup>6</sup>R<sup>7</sup> (wherein E and  
l are the same as defined above, R<sup>6</sup> and R<sup>7</sup> combine together with the nitrogen  
atom to which they bond to form a 5- or 6-membered saturated heterocyclic  
group which may be intervened or not with a nitrogen atom, an oxygen atom or  
a sulfur atom, wherein said heterocyclic group is pyrrolidiny, piperidiny,  
15 piperaziny, morpholino or thiomorpholino, and said heterocyclic group may  
optionally be substituted by a lower alkyl group, a lower alkanoyl group or a  
lower alkoxycarbonyl group), or a salt thereof.

17. The benzoheterocyclic compound according to claim 7, wherein  
R<sup>3</sup> is hydrogen atom, R is a group of the formula: -NHRA (R<sup>A</sup> is the same as  
20 defined in claim 1), R<sup>2</sup> is hydroxy group, a carboxy-substituted lower alkyl  
group or a hydroxy-substituted lower alkyl group, or a salt thereof.

18. The benzoheterocyclic compound according to claim 8, wherein  
R<sup>3</sup> is hydrogen atom, R is a group of the formula: -NHRA (R<sup>A</sup> is the same as  
defined in claim 1), R<sup>2</sup> is hydrogen atom, oxo group, a lower alkylidene group,  
25 a lower alkoxy group, a lower alkenyloxy group, a hydroxy-substituted lower  
alkoxy group, a lower alkoxycarbonyl-substituted lower alkoxy group, a  
carboxy-substituted lower alkoxy group, a lower alkylsulfonyloxy-substituted  
lower alkoxy group, a phthalimide-substituted lower alkoxy group, a group of  
the formula: -O-D-(CO)<sub>l</sub>NR<sup>4</sup>R<sup>5</sup> (wherein D is a lower alkylene group, l is 0 or 1,

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R<sup>4</sup> and R<sup>5</sup> are the same or different and are hydrogen atom, a lower alkyl group, a lower alkanoyl group, a cycloalkyl group, or an amino-substituted lower alkyl group which may optionally have a lower alkyl substituent, or R<sup>4</sup> and R<sup>5</sup> may combine together with the nitrogen atom to which they bond to form a 5- or 6-membered saturated heterocyclic group which may be intervened or not with a nitrogen atom, an oxygen atom or a sulfur atom, wherein said heterocyclic group may optionally be substituted by a lower alkyl group or a lower alkanoyl group), a lower alkanoyloxy-substituted lower alkyl group, a lower alkoxycarbonyl-substituted lower alkyl group, an amino which may optionally be substituted by a lower alkyl group or a cycloalkyl group, a lower alkylsulfonyloxy-substituted lower alkyl group, a phthalimide-substituted lower alkyl group, an imidazolyl-substituted lower alkyl group, a 1,2,4-triazolyl-substituted lower alkyl group, an amino-substituted lower alkanoyloxy group which may optionally have a lower alkyl substituent, or an imidazolyl-substituted lower alkoxy group, or a salt thereof.

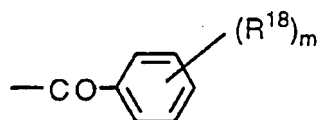
19. The benzoheterocyclic compound according to claim 8, wherein R<sup>3</sup> is hydrogen atom, R is a group of the formula: -NHRA (R<sup>A</sup> is the same as defined in claim 1), R<sup>2</sup> is a group of the formula: -E-(CO)<sub>n</sub>NR<sup>6</sup>R<sup>7</sup> (wherein E and I are the same as defined in claim 1, R<sup>6</sup> and R<sup>7</sup> are the same or different and are hydrogen atom, a lower alkyl group, an amino-substituted lower alkyl group which may optionally have a lower alkyl substituent, or a lower alkanoyl group), or a salt thereof.

20. The benzoheterocyclic compound according to claim 8, wherein R<sup>3</sup> is hydrogen atom, R is a group of the formula: -NHRA (R<sup>A</sup> is the same as defined in claim 1), R<sup>2</sup> is a group of the formula: -E-(CO)<sub>n</sub>NR<sup>6</sup>R<sup>7</sup> (wherein E and I are the same as defined above, R<sup>6</sup> and R<sup>7</sup> combine together with the nitrogen atom to which they bond to form a 5- or 6-membered saturated heterocyclic group which may be intervened or not with a nitrogen atom, an oxygen atom or a sulfur atom, wherein said heterocyclic group is pyrrolidinyl, piperidinyl,

piperazinyl, morpholino or thiomorpholino, and said heterocyclic group may optionally be substituted by a lower alkyl group, a lower alkanoyl group or a lower alkoxy-carbonyl group), or a salt thereof.

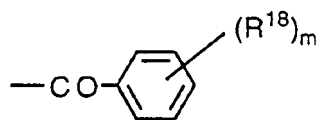
21. The benzoheterocyclic cyclic compound according to claim 8,  
 5 wherein  $R^3$  is hydrogen atom, R is a group of the formula:  $-NHR^A$  ( $R^A$  is the same as defined in claim 1),  $R^2$  is hydroxy group, a carboxy-substituted lower alkyl group or a hydroxy-substituted lower alkyl group, or a salt thereof.

22. The benzoheterocyclic compound according to any one of  
 10 claims 14 to 21, wherein  $R^A$  is a group of the formula:



(in which  $R^{18}$  is a lower alkyl group or a halogen atom, and m is 1), or a salt thereof.

15 23. The benzoheterocyclic compound according to any one of claims 14 to 21, wherein  $R^A$  is a group of the formula:



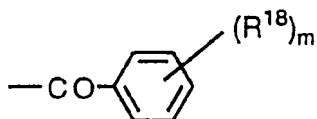
20 (in which  $R^{18}$  is hydrogen atom, a lower alkoxy group, nitro group, a lower alkoxy-carbonyl group, carboxy group, a lower alkoxy-carbonyl-substituted lower alkoxy group, a hydroxy-substituted lower alkoxy group, a carboxy-substituted lower alkoxy group, a lower alkylsulfonyloxy-substituted lower alkoxy group, a phthalimide-substituted lower alkoxy group, or a group of the formula:

25  $-O-E-(CO)_lNR^{19}R^{20}$  (E and l are the same as defined above,  $R^{19}$  and  $R^{20}$  are the same or different and are hydrogen atom or a lower alkyl group, or  $R^{19}$  and  $R^{20}$  may combine together with the nitrogen atom to which they bond to form a 5- or 6-membered saturated heterocyclic group which may be intervened or not with a nitrogen atom or an oxygen atom, wherein said heterocyclic group may

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optionally be substituted by a lower alkyl group, or an amino group which may optionally be substituted by a lower alkanoyl group), and m is 1), or a salt thereof.

24. The benzoheterocyclic compound according to any one of  
5 claims 14 to 21, wherein R<sup>A</sup> is a group of the formula:



- (in which R<sup>18</sup> is the same as defined in claim 1, and m is 2 or 3), or a salt  
10 thereof.

25. The benzoheterocyclic compound according to any one of  
claims 14 to 21, wherein R<sup>A</sup> is thienylcarbonyl group, a cycloalkylcarbonyl  
group or a phenyl-lower alkanoyl group which may optionally have a lower  
alkyl substituent on the phenyl ring, or a salt thereof.

- 15 26. The benzoheterocyclic compound according to claim 1, which is  
7-chloro-5-[N-methyl-N-(2-diethylaminoethyl)amino]carbonylmethyl-1-[6-(2-  
methylbenzoylamino)nicotinoyl]-2,3,4,5-tetrahydro-1H-benzazepine.

27. The benzoheterocyclic compound according to claim 1, which is  
7-chloro-5-carboxymethyl-1-[6-(2-bromobenzoylamino)nicotinoyl]-2,3,4,5-  
20 tetrahydro-1H-benzazepine.

28. The benzoheterocyclic compound according to claim 1, which is  
7-chloro-5-(2-hydroxyethyl)-1-[6-(2-methylbenzoylamino)nicotinoyl]-2,3,4,5-  
tetrahydro-1H-benzazepine.

29. The benzoheterocyclic compound according to claim 1, which is  
25 7-chloro-5-(2-acetylaminoethyl)-1-[6-(2-methylbenzoylamino)nicotinoyl]-  
2,3,4,5-tetrahydro-1H-benzazepine.

30. The benzoheterocyclic compound according to claim 1, which is  
7-chloro-5-hydroxy-1-[5-(2-methylbenzoylamino)-2-thiazolylcarbonyl]-2,3,4,5-  
tetrahydro-1H-benzazepine.

- 30 31. An vasopressin antagonist, which comprises as an active

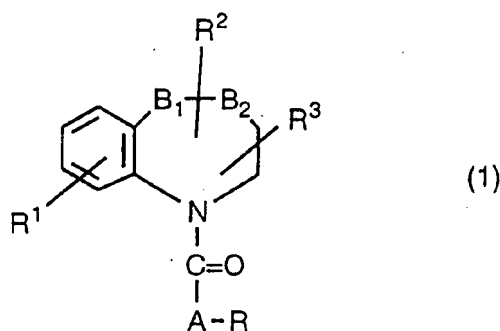


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ingredient a benzoheterocyclic compound as set forth in claim 1, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable carrier or diluent.

32. An oxytocin antagonist, which comprises as an active ingredient a benzoheterocyclic compound as set forth in claim 1, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable carrier or diluent.

33. A process for preparing a benzoheterocyclic compound of the formula (1):



wherein R<sup>1</sup> is hydrogen atom or a halogen atom,

R<sup>2</sup> is hydrogen atom, oxo group, a lower alkylidene group, hydroxy group, a lower alkoxy group, a lower alkenyloxy group, a hydroxy-substituted lower alkoxy group, a lower alkoxy carbonyl-substituted lower alkoxy group, a carboxy-substituted lower alkoxy group, a lower alkylsulfonyloxy-substituted lower alkoxy group, a phthalimide-substituted lower alkoxy group, a hydroxy-substituted lower alkyl group, a group of the formula: -O-D-(CO)<sub>l</sub>NR<sup>4</sup>R<sup>5</sup>

(wherein D is a lower alkylene group, l is 0 or 1, R<sup>4</sup> and R<sup>5</sup> are the same or different and are hydrogen atom, a lower alkyl group, a lower alkanoyl group, a cycloalkyl group, or an amino-substituted lower alkyl group which may optionally have a lower alkyl substituent, or R<sup>4</sup> and R<sup>5</sup> may combine together with the nitrogen atom to which they bond to form a 5- or 6-membered saturated heterocyclic group which may be intervened or not with a nitrogen atom, an oxygen atom or a sulfur atom, wherein said heterocyclic group may

optionally be substituted by a lower alkyl group or a lower alkanoyl group), a group of the formula:  $-E-(CO)_lNR^6R^7$  (wherein  $l$  is the same as defined above,  $E$  is a lower alkylene group,  $R^6$  and  $R^7$  are the same or different and are hydrogen atom, a lower alkyl group, an amino-substituted lower alkyl group which may optionally have a lower alkyl substituent, or a lower alkanoyl group, or  $R^6$  and  $R^7$  may combine together with the nitrogen atom to which they bond to form a 5- or 6-membered saturated heterocyclic group which may be intervened or not with a nitrogen atom, an oxygen atom or a sulfur atom, wherein said heterocyclic group may optionally be substituted by a lower alkyl group, a lower alkanoyl group or a lower alkoxycarbonyl group), a lower alkanoyloxy-substituted lower alkyl group, a lower alkoxycarbonyl-substituted lower alkyl group, an amino which may optionally be substituted by a lower alkyl group or a cycloalkyl group, a carboxy-substituted lower alkyl group, a lower alkylsulfonyloxy-substituted lower alkyl group, a phthalimide-substituted lower alkyl group, an imidazolyl-substituted lower alkyl group, a 1,2,4-triazolyl-substituted lower alkyl group, an amino-substituted lower alkanoyloxy group which may optionally have a lower alkyl substituent, or an imidazolyl-substituted lower alkoxy group,

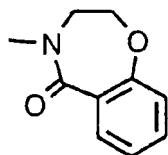
$R^3$  is hydrogen atom, a lower alkoxy group or a hydroxy-substituted lower alkyl group,

$B_1$  and  $B_2$  are each methylene group or a group of the formula:  $-NR^8-$  (wherein  $R^8$  is hydrogen atom or a lower alkyl group),

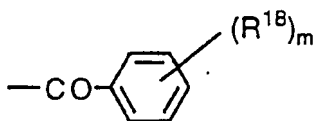
$A$  is a 5- or 6-membered unsaturated heterocyclic residue having 1 to 2 heteroatoms selected from an oxygen atom, a nitrogen atom and a sulfur atom, and

$R$  is a group of the formula:  $-NHR^A$  or a group of the formula:

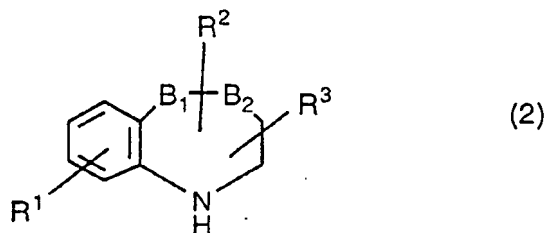
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5 wherein  $R^A$  is a group of the formula:

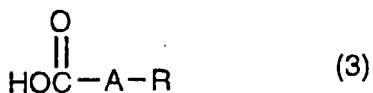


[wherein  $m$  is an integer of 1 to 3,  $R^{18}$  is hydrogen atom, a lower alkyl group, a lower alkoxy group, a halogen atom, nitro group, a lower alkoxycarbonyl group, carboxy group, a lower alkoxycarbonyl-substituted lower alkoxy group, a hydroxy-substituted lower alkoxy group, a carboxy-substituted lower alkoxy group, a lower alkylsulfonyloxy-substituted lower alkoxy group, a phthalimide-substituted lower alkoxy group, or a group of the formula:  $-O-E-(CO)_lNR^{19}R^{20}$  (wherein  $E$  and  $l$  are the same as defined above,  $R^{19}$  and  $R^{20}$  are the same or different and are hydrogen atom or a lower alkyl group, or  $R^{19}$  and  $R^{20}$  may combine together with the nitrogen atom to which they bond to form a 5- or 6-membered saturated heterocyclic group which may be intervened or not with a nitrogen atom or an oxygen atom, wherein said heterocyclic group may optionally be substituted by a lower alkyl group, or an amino group which may optionally be substituted by a lower alkanoyl group)], thienylcarbonyl group, a cycloalkylcarbonyl group or a phenyl-lower alkanoyl group which may optionally have a lower alkyl substituent on the phenyl ring, or a salt thereof, which comprises reacting a benzoheterocyclic compound of the formula (2):



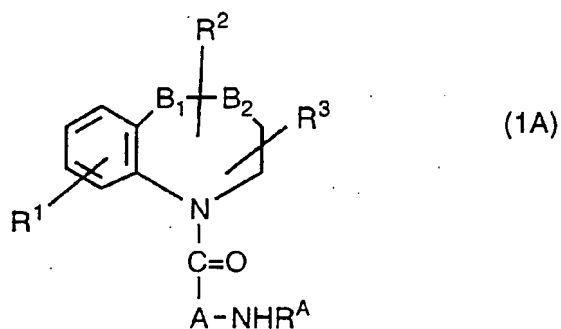
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wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $B_1$  and  $B_2$  are the same as defined above, with a carboxylic acid of the formula (3):

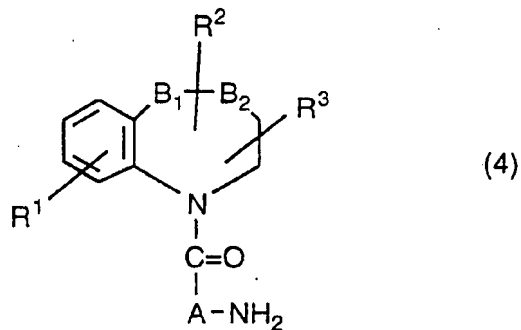


5 wherein A and R are the as defined above, by a conventional amido bond producing reaction.

34. A process for preparing a benzoheterocyclic compound of the formula (1A):



15 wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $B_1$ ,  $B_2$ , A and  $R_A$  are the same as defined above, or a salt thereof, which comprising reacting a compound of the formula (4):



20 wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $B_1$ ,  $B_2$  and A are the same as defined above, with a compound of the formula (5):



wherein  $R^A$  is the same as defined above.

## INTERNATIONAL SEARCH REPORT

International Application No

PC1/JP 93/01082

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 5 C07D401/06 A61K31/55 C07D401/14 C07D409/14 C07D409/06  
 C07D417/06 C07D405/06 C07D413/14 C07D417/14

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,91 05549 (OTSUKA PHARMACEUTICAL CO.) 2 May 1991 cited in the application see the whole document ---	1-32
P,A	EP,A,0 514 667 (OTSUKA PHARMACEUTICAL CO.) 25 November 1992 see the whole document -----	1-32

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents :

- \* "A" document defining the general state of the art which is not considered to be of particular relevance
- \* "E" earlier document but published on or after the international filing date
- \* "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \* "O" document referring to an oral disclosure, use, exhibition or other means
- \* "P" document published prior to the international filing date but later than the priority date claimed

\* "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\* "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\* "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\* "A" document member of the same patent family

Date of the actual completion of the international search

5 November 1993

Date of mailing of the international search report

30. 11. 93

Name and mailing address of the ISA

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 Fax (+31-70) 340-3016

Authorized officer

HEYWOOD, C

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP 93/01082

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
  
Claims searched incompletely: 1 - 24, 31, 32 - 34  
  
./.
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
  
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
  
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/

The definition of the following substituent(s) is too general and /or encompasses too broad a range of totally different chemical groups, only partly supported by examples given in the descriptive part of the application:

Heterocyclic rings within claim 1, etc.

The vast number of theoretically conceivable compounds resulting from the combination of all claimed substituents of above list precludes a comprehensive search. Guided by the spirit of the application and the inventive concept as disclosed in the descriptive part of the present application the search has been limited to the following case(s): As illustrated in the examples.

(Art. 6 and Rule 33 - PCT; Guidelines Exam. Part. B, Chapt. III, 3.6,3.7)

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 93/01082

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9105549	02-05-91	AU-B- 630284	22-10-92
		AU-A- 7291791	19-12-91
		EP-A- 0450097	09-10-91
		CN-A- 1051038	01-05-91
		JP-A- 4154765	27-05-92
<hr/>			
EP-A-0514667	25-11-92	AU-A- 1498492	22-10-92
		CN-A- 1066653	02-12-92
		JP-A- 5132466	28-05-93
		US-A- 5244898	14-09-93
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